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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

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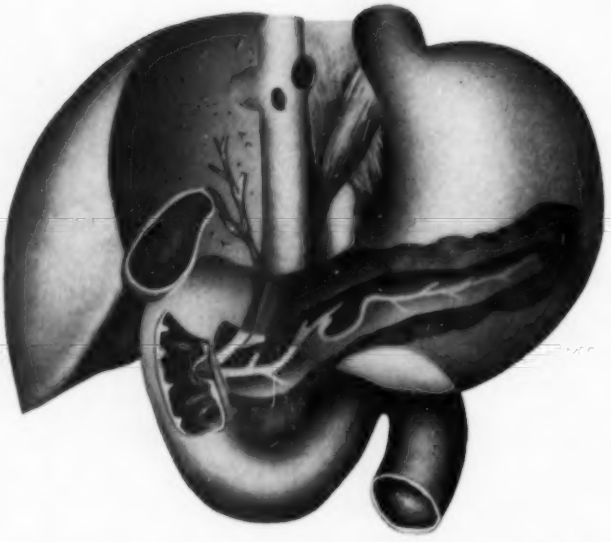

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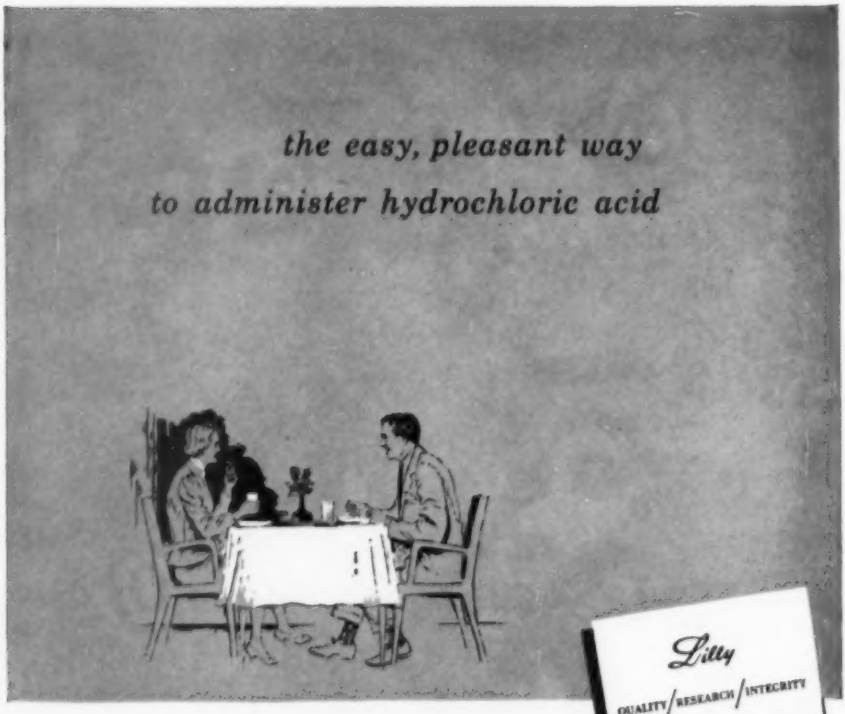

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ROBERT L. CRAIG, *Editor*

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† Deceased March 24, 1955.

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VIRAL HEPATITIS*

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VIRAL hepatitis represents one of the most important problems in the field of infectious diseases today. The military aspects have been frequently emphasized. These include loss of time, prolonged hospitalization and prolonged convalescence, and are also important, although perhaps not as pressing, in civil life, not only in this country but throughout the whole world. The number of articles appearing in medical publications, upwards of 2,000 during the past five years, indicates the concern of the writers with these matters and deal particularly with epidemiology, prevention and treatment.

The control of infectious diseases can be extremely difficult when the etiological agent cannot be isolated. This is well illustrated in the case of both infectious hepatitis (Virus A) and homologous serum hepatitis (Virus B).

Although a considerable amount of work has been done during and since World War II, and much valuable information has been obtained,

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, October 20, 1954.
From the Laboratory of Biologics Control, National Microbiological Institute, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Md.

there have been few significant advances in knowledge concerning the etiology, specific diagnosis or treatment of these diseases. The main difficulty or bar to the acquisition of firm information resides in the fact that it has not been possible thus far to transmit the illness to animals other than man or to develop any serological or other specific tests for the agents or to identify specific antibodies. A great many attempts have been made to adapt the agent(s) to some animal and to pass them in the chick embryo or tissue cultures with negative or at most doubtful results. A review of what has been done and an evaluation of the results obtained in these directions has recently been attempted in a symposium held under the joint sponsorship of the National Research Council and of the Commission on Virus and Rickettsial Diseases of the Armed Forces Epidemiological Board.[1] The general conclusion was that in no case could it be proved beyond question that adaptation or passage had been achieved. It is generally felt that progress in obtaining knowledge about these illnesses will not be great until some laboratory methods of detecting or propagating the agents are devised. For a rather succinct discussion and review of the information available, reference may be made to the First Report of the Expert Committee on Hepatitis of the World Health Organization[2] or a recent review by Dr. F. O. MacCallum in the British Medical Bulletin which covered essentially similar ground.[3]

The fact that both viruses may be transmitted by inoculation and that the illnesses produced are for the most part similar suggests that they may be related. Both have been demonstrated to pass through filters capable of removing bacteria, and in the case of Virus B, material which was passed through a gradocol membrane of average pore size 52 mu remained infectious, indicating a dimension (in one direction at least) of 26 mu or less.[4] These viruses appear to be unusually resistant to inactivation by physical and chemical agents. This has certainly been demonstrated in the case of Virus B which is able to withstand applications of heat or ultraviolet energy at levels many times that required for the inactivation of most other viruses. In the case of Virus A the mode of transmission is usually by the fecal-oral route, but it can also be transmitted parenterally. In the case of Virus B, although Iablokowa,[5] Shank and Mirick as quoted by Aycock and Oren[6] and Bradley[7] have observed clinical situations which suggest the contact transmission of this infection, the parenteral route is the only one which has been demonstrated conclusively. There are certain clinical differences which

characterize the illness produced by the agents, which, while they may not be too helpful in making a differential diagnosis in individual cases, are nevertheless apparent when a large number of cases are studied. The incubation period for Virus A is usually in the range fifteen to forty days while that for serum hepatitis is sixty to 160 days.[2] Onset is usually febrile and acute in the case of the former while it is usually insidious and afebrile in the case of the latter. There are also some suggestive differences in the changes noted in the liver function tests during the course of the illness. Some immunological differences have also been demonstrated. There is apparently no heterologous immunity between the two. Homologous immunity has been demonstrated in the case of Virus A[8] and this fact is put to good and practical advantage in the prophylactic use of gamma globulin. Attempts to show protection with gamma globulin prepared from the blood of convalescents from Virus B infection have failed.[9] However, the fact that not all persons who receive inoculations of icterogenic material develop hepatitis, while others who have had hepatitis may withstand homologous challenge, suggests that the actual situation here may not be simple.

The question of incubation period may be linked with immunological factors. MacCallum[3] has recently made a suggestion which could explain the apparently anomalous findings which have been reported where known icterogenic material may cause short incubation hepatitis in one recipient and long incubation hepatitis in another. As an example, if the donor's blood contained both Virus A and B, it would cause long incubation hepatitis in a person immune to A, short incubation hepatitis in a person immune to B and either short or long in a person with immunity to neither.

The long incubation period and apparent absence of antibodies in the case of Virus B infections have given rise to a great deal of speculation. A recent suggestion is that of Burnet[10] who considers the implications of transplacental transmission at a time when the embyro is unable to distinguish between what he terms "self" and "non-self" proteins.

Carriers undoubtedly constitute the primary source of infection for both Virus A and Virus B. The information available concerning carriers is far from adequate; but even so it is somewhat more extensive in the case of Virus B. It is widely recognized that cases of homologous serum hepatitis develop following the administration of blood from donors who were in good health at the time of collection of the blood

TABLE I.—RESULTS OF INOCULATION OF VOLUNTEERS WITH SERUM FROM SUSPECTED DONORS

Case	Donor	Days Since Incriminated Donation	No. Volunteers Inoc.	Cases of Hepatitis: Jaundice With	Cases of Hepatitis: Jaundice Without	Cases of Hepatitis: Total	Incubation Period (days): In Volunteers(c)	Incubation Period (days): Original Recipient
1	W.C.	203	10	0	0	0	—	65
2	L.H.	385	10	4	2(a)	6	(18),30,45,46,(46),56	48
			5	0	1	1	(43)	
3	V.S.	356	10	1	0(a)	1	48	40
5	R.F.	149	10	1	0(a)	1	84	70
7	H.H.	135	10	4	0	4	35,50,56,72	
			5	5	—	5	43,49,56,57,63	44
8	C.D.	43	10	2	1(b)	3	(50),57,67	32

(a) One additional subject in each of these groups showed development of equivocal or abnormal hepatic tests suggestive of hepatitis without jaundice.
(b) Three additional subjects in each of these groups showed development of equivocal or abnormal hepatic tests suggestive of hepatitis without jaundice.
(c) Incubation periods in parenthesis refer to cases of hepatitis without jaundice.

Reprinted by permission, in modified form, from article by Murray et al.,[10] in *J. Amer. med. Assoc. 154*:1072-74, 1954.

and had been screened with this possibility in mind. Stokes et al.[11] have produced evidence that there are carriers of both infectious hepatitis and serum hepatitis. In one of the instances cited, there was circumstantial evidence at least that a carrier of Virus B remained infective for as long as five years. Neefe et al.[12] studied a number of suspected carriers with a view to characterizing them from the point of view of their liver function. Inoculation of sera from six of these suspected carriers into volunteers by Murray et al.[13] clearly demonstrated that five of the six were in fact carriers. The results obtained in this study are summarized in Table I (taken from this paper) and illustrate a number of facts concerning the transmission of hepatitis.

1. Five of the six serums studied were icterogenic.
2. Two of these caused a relatively large number of cases among those inoculated, 7/15 (46.7 per cent) in one and 9/15 (60 per cent) in another.
3. Two resulted in single cases.
4. The incubation periods of the illnesses produced in the volunteers corresponded in general with those noted in the original recipients. It should be noted that many of these were shorter

than the usual 60-100 days given for Virus B. The reasons for these differences are not apparent. It is possible that strain differences may be operating, that the infectious titer may be the explanation or perhaps some unusual relationship between the infecting organism and antibodies to it. Since no information is available on these facts, it is idle to speculate upon them beyond mentioning the possibilities.

5. It was demonstrated that a carrier may be infective for as long as 385 days.

The fact that cases of hepatitis with relatively short incubation periods have been encountered in the case of carriers and are often seen after the administration of whole blood strongly suggests that some of the hepatitis transmitted by inoculation may in fact be infectious hepatitis (Virus A). The cases encountered following the administration of pooled plasma almost invariably have longer incubation periods. It has been suggested that one possible reason for this is the fact that antibodies for infectious hepatitis (Virus A) may be relatively common in the population and their presence in pooled plasma would tend to neutralize or modify any infectious hepatitis virus which may be present. The very excellent evidence that gamma globulin is effective in the prophylaxis of infectious hepatitis indicates that antibodies to this agent must be fairly common in our population.

No information is available concerning the number of individuals who may be carriers of Virus A. In the case of Virus B, it is possible to arrive at an indirect estimate by a review of transfusion records. The best estimate, based upon a review of the available literature, for the incidence of hepatitis following whole blood transfusions, uncomplicated by simultaneous administration of pooled plasma, is between 0.3 and 0.5 per cent. In trying to relate this estimate to the number of carriers involved we must consider two circumstances which tend to affect this figure in opposite ways: 1) The administration of whole blood is seldom restricted to single transfusions so that we should perhaps say 0.3 to 0.5 per cent of those who receive blood transfusions may develop hepatitis with the understanding that most recipients are given more than one unit of blood; 2) Only about one-half of those who receive icterogenic material develop hepatitis. We have noted above that our studies with carriers resulted in rates from 10 per cent to 60 per cent. A review of subjects who received the infected plasma which we used

in many of our studies on the safety of blood products[14,15] indicated that approximately 52 per cent developed hepatitis. Approximately 12 per cent of these cases were anicteric and would in all probability have been missed were it not for the close scrutiny which these subjects received. Evaluation of reported figures where multiple cases of hepatitis have resulted from the administration of a certain lot or batch of material has been difficult; adequate follow-up is in most cases next to impossible. A rate of 50 per cent appears to be realistic.

The potential infectivity of icterogenic material is high. A figure of 0.02 ml. has been quoted as being capable of transmitting infection.[2] Our own studies provide indirect information in this regard by which a figure may be deduced by considering the pool of infected plasma which was used in a great deal of this work.[15] The pool consisted of 130 liters of plasma and was prepared by the addition of approximately one liter of plasma or serum collected from subjects in the acute phase of their illness to the plasma drawn off from some 408 commercially obtained bleedings. It is possible that some of these may have been icterogenic themselves. The final pool proved to be icterogenic and capable of producing infection in a dose of 1.0×10^{-4} ml. If we take into account the expected occurrence of carriers, two of the 408 bloods mentioned above could have come from carriers. Two average donations would provide approximately 500 ml. of plasma so that the 130 liters probably contained approximately 1.5 liters of icterogenic plasma. In all probability the virus titer in each of the separate icterogenic materials added to the pool differed. However, we can say that the initial dilution was approximately 1/100 and with an infective dose of 1.0×10^{-4} ml. the average original icterogenic material had an infective dose of approx. 1.0×10^{-6} ml. and if the titer of the various component materials varied much, some may have had a smaller infective dose. A recent study by Drake et al.[16] showed infectivity with 1/40 x this amount or 4.0×10^{-5} ml. This represents a very small amount of blood or plasma. So small in fact that the amount remaining on an instrument even after vigorous washing and meticulous cleansing might be infective.

General Prevention and Control

In the case of infectious hepatitis, presumably spread by the fecal-oral route, control depends in the main upon breaking the cycle of transmission. This is difficult to accomplish with any degree of security in

the case of a disease where we cannot isolate the etiological agent. In general, the precautions to be taken are those which one would apply in the case of typhoid. Gamma globulin has been shown to be effective as a prophylactic and should be used in family and institution groups.

Prevention of Parenteral Transmission: There is ample evidence in the literature that parenteral transmission takes place. Aside from the well known examples of plasma, serum and blood transfusion as well as the experience with serum-stabilized yellow-fever vaccine in World War II,[17] cases of hepatitis have been reported following malaria therapy,[18, 19] in diabetic clinics,[20, 21] following arsenotherapy[22] and chrysotherapy,[7] following venipuncture and other blood-letting procedures as well as following immunization.[23] Inadvertent infections have been noted in laboratory technicians.[24-27] It has also been reported following dental procedures[28] and non-medical activities such as tattooing[29-32] and as occurring among drug addicts.[33, 34] A number of blood derivatives including plasma, fibrinogen,[35] thrombin[36, 37] and fraction IV[38] have been shown capable of transmitting hepatitis. Control measures should be directed towards:

1. Prevention of inadvertent transmission by inadequately sterilized instruments
2. Selection of blood donors
3. Sterilization of blood and blood products.

Sterilization of Instruments: It is important to use an effective means of sterilization. While some chemical agents may be effective there is little certain information about their action. There is no evidence that any of the commonly used antiseptics such as alcohol, ether, zephiran, etc. are capable of inactivating Virus B. Heat, applied either by boiling or by autoclaving, has proved effective in practice. The section of the Minimum Requirements of the National Institutes of Health for Citrated Whole Blood[39] dealing with the sterilization of instruments calls for boiling for thirty minutes or autoclaving at 121° C. (15 lbs. pressure) for twenty minutes. Sterilization should be preceded by thorough washing to prevent organic material coagulating or drying on the instrument surfaces and thus interfering with the sterilizing process. The report of the Expert Committee of the World Health Organization referred to above recommended hot air sterilization at 170° C. for thirty minutes if the sterilizer could be properly controlled but preferably 180° C. for one hour. Autoclaving was recommended but the conditions were not

specified. Boiling in water for at least ten minutes was considered acceptable. The information which we have concerning the thermal death point of the agent is rather limited. Gellis et al.[40] have demonstrated that a mixture consisting of 40 ml. of normal serum albumin and 10 ml. of proved icterogenic plasma which had been heated at 60° C. for ten hours failed to produce hepatitis in 10 ml. amounts when inoculated into five volunteers.

Portions of the plasma pool referred to above were subjected to controlled heating and icterogenic activity was still clearly present after four hours at 60° C.[14] Five of ten volunteers who received 1.0 ml. doses of such heated material developed hepatitis. The average incubation period was slightly longer than that of cases developing from unheated plasma indicating that there was perhaps some reduction in infectivity.

Heating at 60° C. for four hours represents rigorous treatment for any microorganism and the fact that the agent of serum hepatitis survived this temperature should be accepted as indicating caution about the manner in which instruments are sterilized.

More is needed than the actual process of sterilization in order to minimize the danger of parenteral transmission. Our mental approach to the subject is important. Although the simple matter of using a separately sterilized needle and syringe for venipunctures or parenteral inoculations would seem to solve part of the problem, there is considerable reluctance among many physicians to abandon the convenient but inadequate method of using separate needles with a single syringe and a number of ingenious devices have been invented to prevent back-flow and so permit the continued use of this procedure. In view of the demonstrated potentially high infectivity of some blood one must assume that the danger still exists. The increasing use of disposable single-use instruments is encouraging. Another possible source of danger is the multiple dose container, the contents or stopper of which may become contaminated if meticulous syringe procedures are not followed. Packages of biologics are now required to carry a warning statement in this respect.

Selection of Blood Donors: Present requirements for the screening of blood donors call for the elimination of donors with a history of hepatitis, donors with close contact during the preceding six months with individuals having viral hepatitis and donors who themselves received a blood or plasma transfusion during the preceding six months.

Obviously, these measures are not completely effective as cases of hepatitis still occur following blood transfusion. This circumstance does not appear to be a valid reason for abandoning these screening procedures, however. In examining the carriers discussed earlier, Neefe et al.[12] were impressed with the number of these individuals who had abnormal liver function tests, particularly abnormal thymol turbidity levels. The suggestion has been made that the institution of this test for screening might be helpful. A number of attempts have been made in this direction but no clear-cut indication of any advantage to the institution of this measure has as yet emerged. Contributing factors to this are: 1) Frequent occurrence of abnormal thymol turbidity levels in the presumably normal population, running as high as 15 per cent whereas the carriers probably do not exceed 0.5 per cent and we could only expect to exclude a fraction of these at best; 2) The fact that large numbers of bloods collected are chylous which in itself results in an elevation of the thymol turbidity in some instances; 3) The reluctance of those responsible for operating blood banks to accept a rejection rate as high as 15 per cent. The method is nevertheless worthy of serious consideration even if it is only partially effective as a means of excluding potential carriers.

Sterilization of Blood Products

Plasma Pool Size: Knowing that carriers do occur, and that approximately 0.5 per cent of those who receive whole blood collected from donors who have been adequately screened by present standards, indicates that the danger of infection from any pool of plasma prepared from such bloods depends, among other things, on the number of units entering into it. It is obvious that a "statistical" method of reducing the danger would be to reduce the number of units in each pool of plasma. The ultimate in this direction would, of course, be single donor plasma. This, however, presents an additional problem, namely that of cross matching before administration. It limits the usefulness of such a product under disaster conditions. A number of blood banks are, however, preparing plasma of this character. Difficulties related to cost, handling and bacterial contamination are increased by decreasing the size of the pools as far as the commercial production of plasma is concerned.

Ultraviolet Irradiation: Early hopes for the effectiveness of ultraviolet radiation as a method of eliminating or reducing the hazard of serum hepatitis, at least in the case of serum, led to its introduction as

a means of freeing plasma of the virus of serum hepatitis. A special feature of this method was that the plasma proteins appeared to be unaffected by the amount of ultraviolet energy used. A number of reports now indicate that cases are being encountered even with materials which it was believed had been rendered safe. A rate as high as 11.9 per cent was reported in one series of recipients who had been carefully followed for at least six months.[41]

Three studies on the effect of ultraviolet light were carried out by our group using material from the infected plasma pool which has been described.[15] The irradiators studied were (a) the Dill Irradiator, (b) the Habel-Sockrider Irradiator, and (c) the Oppenheimer-Levinson Centrifugal Filmer. In all instances particular attention was paid to the measurement of the U. V. output of the lamps used, to continuous monitoring of each irradiation run and to the accurate measurement of the rate of flow of the plasma through the apparatus. Cases of hepatitis occurred following inoculation into volunteers of all materials run at practical levels of irradiation, the exceptions being plasma which had been passed through the Habel-Sockrider apparatus five or more times, treatment which resulted in definitely detectable changes in the plasma proteins. The studies with the Dill Irradiator were performed first because this type of apparatus was most widely used. When sterilization of the infected plasma was not achieved even at 3 times the level of irradiation used commercially an attempt was made to verify, if possible, the results of the work of Blanchard et al.[42] with the identical apparatus used by these authors. The Oppenheimer-Levinson apparatus was studied because it possesses the feature of being able to present an extremely thin film of plasma for irradiation. These results were certainly most discouraging. Ultraviolet irradiation is a difficult process to apply with certainty and the above results may mainly reflect the inadequacy of design of the irradiators used. However, these were the only types available for commercial use at the time these studies were conducted.

A number of rather interesting and perhaps significant features were noted in examining the records of the individuals who developed hepatitis in the course of this particular study.

1. A lengthening of the incubation period.
2. A lessening in the severity of the illness encountered in terms of duration of illness (based upon abnormal laboratory findings)

and maximum total serum bilirubin levels reached during the course of the illness.

These findings strongly suggest that even though ultraviolet irradiation is not completely effective with the types of irradiating apparatus generally available, it must have some effect on the virus present. In addition, of course, it is an excellent means of destroying live bacteria and has a valuable function in this respect.

Room-Temperature Storage: Room-temperature storage of plasma has recently received considerable support as a means of reducing the hazard of hepatitis. This stems largely from the reports by Allen and his co-workers.[43] An attempt to determine the efficacy of this method was made, utilizing portions of the infected plasma pool which we have previously described.[44] One out of 19 volunteers who received plasma stored at 70° C. for six months developed hepatitis. This case was unusual because of the long incubation period, but the fact that it was possible to transmit hepatitis by means of blood taken from him in the acute phase indicates that this actually was a case of hepatitis. One must conclude from this that the infectivity of the plasma had been considerably reduced by storage for six months. The evaluation of the significance of the one case presents a problem. Had further cases occurred one could say with a fair degree of certainty that the material did contain the hepatitis virus. One case, however, does not constitute absolute proof of failure of inactivation. In the case of plasma stored for three months under the same conditions, three of five volunteers inoculated developed hepatitis; incubation periods were eighty-two, ninety-five and 117 days. This indicates that the agent we are dealing with is quite resistant to inactivation by this means. This method of inactivation may have limited applicability because of the hazard of bacterial contamination (psychrophilic organisms must be taken into consideration here)[45, 46] although Allen's own experience in this regard has been favorable. Furthermore, there is considerable alteration of the plasma proteins other than the albumin component.

Immune Serum Globulin: The Minimum Requirements of the National Institutes of Health for Immune Serum Globulin have in the past stipulated that pools consist of at least 500 individual contributions; present requirements call for 1,000. In view of the estimated number of blood donors who are carriers, it might be expected that many of the pools of plasma used in the manufacture of immune serum globulin

would be infected. General experience indicates that the incidence of homologous serum hepatitis following administration of immune serum globulin must be low. Cockburn[47] has reported the development of one case of hepatitis among fifty-eight subjects inoculated with immune serum globulin produced by ether fractionation. The plasma used in its preparation gave rise to seven cases of hepatitis among ten children who were given from 5 to 30 ml. parenterally.

Immune serum globulin was one of the products prepared from the infected pool plasma.[48] This was administered to ten volunteer subjects in 2.0 ml. doses. Simultaneously, five volunteers in a control group each received 1.0 ml. of the original plasma from which the globulin had been produced. None of the subjects who received globulin developed hepatitis, with or without jaundice, while one of the five in the control group developed hepatitis with jaundice having an incubation period of eighty-four days. A second individual in this control group developed positive hepatic tests suggestive of hepatitis without jaundice.

Thrombin: Some vials of thrombin from a commercial lot reported to have caused hepatitis in a number of patients who had received it as a topical application following surgery of various types were investigated. The results of these studies have been reported jointly by Dr. Stokes' group, Philadelphia, and ourselves.[37] The particular lot of thrombin studied proved to be icterogenic. Whether this represents a breaking through the manufacturing process by the virus is not clear. The possibility exists that it may have been introduced by the placental extract used to activate prothrombin to thrombin, a process carried out subsequent to alcohol fractionation.

Albumin: Paine and Janeway[49] after reviewing the records of 237 patients who received albumin intravenously concluded that their findings suggested that the use of human albumin intravenously does not carry the risk of homologous serum jaundice that exists with the use of pooled plasma or serum and to a lesser extent with single donation plasma or whole blood. The safety of albumin was strongly indicated by the studies of Gellis and his associates,[40] previously referred to in connection with the resistance of the agent to heat, and is borne out by studies (unpublished as yet) carried out by our group using albumin prepared from icterogenic plasma by alcohol fractionation followed by heating at 60° C. for ten hours, a required step in the processing of normal serum albumin (human).

TABLE II—EFFECT OF DIET ON DURATION OF ILLNESS

Infecting Material	*No. of subjects*		*Duration of Illness (days)**		*Statistical Evaluation of Differences*
	Special Diet	*Ad lib Diet*	*Special Diet*	*Ad lib Diet*	
Infected Pool Plasma	9	10	90	62	Significant
Infected Pool Plasma, treated	14	15	42	56	Not significant
Carrier Material	8	7	60	39	Not significant
Thrombin	1	3	—	—	
Statistical evaluation of differences			Signif.	Signif.	

* Time in days during which Total Serum Bilirubin (T.S.B.) remained above 1.0 mgm. per cent.

TREATMENT OF HEPATITIS

The results of studies on the effect of diet on the course of hepatitis in sixty-seven volunteers who participated in some of the above investigations have been reported by Leone et al.[50] Of these, thirty-two were in a "special" diet group and thirty-five in an "ad lib" diet group. The former received a diet consisting of 3844 calories (215.2 gm. protein, 79.2 gm. fat and 579.4 gm. carbohydrate) while the diet received by the latter group consisted of 2609 calories (93.8 gm. protein, 90.5 gm. fat and 361.7 gm. carbohydrate).

The cases of hepatitis studied resulted from parenteral inoculation of the following infecting materials which were being studied for the presence of the agent of hepatitis:

A. Infected pool plasma.

B. Infected pool plasma, treated. This represents materials which remained infective after various attempts at inactivation of the virus.

C. Carrier material.

D. Thrombin.

The distribution of the sixty-seven cases between the two diet groups, according to type of infecting material, is summarized in Table II.

The evaluation of the effect of the two diets was made chiefly in terms of the duration of illness of these cases.

The following main results were obtained:

With return to a bilirubin level of 1.0 mgm. per 100 ml. taken as the endpoint of recovery

(a) Subjects who received infected pool plasma and were given the "special" diet had a course of illness which was on the average 23 days longer than the corresponding individuals on the "ad lib" diet. This difference was statistically significant.

(b) Subjects who received infected pool plasma, treated, and were given the "special" diet had a course of illness which was on the average 14 days shorter than corresponding individuals on the "ad lib" diet. This difference did not reach statistical significance.

(c) Subjects who received "carrier material" and were given the "special" diet had a course of illness which was on the average 21 days longer than corresponding individuals on the "ad lib" diet. This difference was not statistically significant.

When the figures were examined to determine the role of the infecting material within each diet group, information of considerable interest emerged. Thus, in this series of cases and with the therapy used the type of inoculum received by the patients played a greater role in determining the course and outcome than did the therapy. Various other criteria for duration and severity of illness were examined with essentially the same findings. In most clinical situations little will be known concerning the nature of the infecting material but one can assume with some reason that there must be considerable heterogeneity as to source and amount of inoculum. A further observation made in the study was that the occurrence of complications was greater in the group which received the "special" diet. These findings indicate that the evaluation of any general type of therapy in the treatment of hepatitis must be approached with great care and planning; they also suggest that conclusions based upon a few cases must be accepted with reservation.

In another recently completed, carefully controlled study of the effects of bed rest and diet in the treatment of infectious hepatitis[51] no demonstrable preference was observed in favor of strict bed rest when compared with "ad lib" activity. A forced high-protein and fat diet had a slight, but statistically significant, favorable effect on the rate of convalescence. The apparent differences between these results and those reported above may have been due to (a) the fact that one group

consisted entirely of cases of homologous serum hepatitis[50] while the other consisted of cases of infectious hepatitis,[51] (b) the cases of serum hepatitis studied could be placed under treatment at a much earlier stage in the course of their illness than was possible in the latter study with cases of infectious hepatitis, and (c) the average severity of the illnesses encountered.

Medical emergencies arising in the course of hepatitis must, of course, be treated on an individual basis. Massive doses of cortisone have been suggested[52] as being life-saving in treatment and management of coma but the information available so far is too scanty to warrant any definite conclusions. The use of cortisone or ACTH[53, 54] apparently causes amelioration of symptoms in some cases as well as a return towards normal in the laboratory findings but presents difficulties in management with the danger of a relapse following withdrawal and there is no certainty that their effect on the total course of illness is appreciable.

Summary

The control of infectious diseases is extremely difficult when the etiological agent cannot be isolated. This is evident with both infectious hepatitis (virus A) and with serum hepatitis (virus B), although the information available concerning the transmission of the latter is more definite. Asymptomatic carriers have been shown to exist in the case of the latter and probably exist in the case of the former. Undoubtedly, they constitute the primary source of infection.

The control of infectious hepatitis rests on (a) the institution of general measures designed to break the cycle of a water-borne, food-borne or person-to-person transmission of infection, and on (b) the prophylactic use of gamma globulin.

In the case of serum hepatitis the control measures are more specifically directed to interrupting the transmission of the agent from person to person by inactivating or eliminating the agent from human blood and blood products used for therapeutic and diagnostic purposes and by preventing the transfer of contaminated blood by means of blood-letting and other instruments. Certainty in these methods of control is complicated by the high infectivity of some sera from individuals harboring the infection (approximately 1.0×10^{-6} ml.) and by the extreme resistance of the agent(s) to destruction by physical or chemical means.

Ultraviolet irradiation has been shown to be ineffective, at least as

performed on a production basis, at levels that do not alter plasma proteins. Room-temperature storage reduces infectivity but the method is not without limitations. The chemical agents which have been tried have been only partially effective. Fractionation by the cold ethanol method produces gamma globulin and albumin which are safe. The latter, however, must be heated at 60° C. for ten hours to eliminate the danger of the transmission of hepatitis. Fibrinogen and thrombin may both be icterogenic. Although careful screening of blood donors on the basis of history and liver function tests undoubtedly may contribute to the reduction of the number of icterogenic bloods which are collected, there is no method available for eliminating the danger from whole blood.

The treatment of uncomplicated hepatitis has depended chiefly on the institution of bed rest and the use of special diets; high-fat, low-fat, and high-protein diets have been recommended at various times. The extreme variability in the severity of the clinical course of hepatitis makes evaluation of any therapeutic measure difficult in the absence of extensive series of cases in which the effects of the therapy being studied have been thoroughly controlled. Recent attempts to evaluate diet and bed rest as therapeutic measures have shown that there may be some slight advantage to a high-protein diet in the case of infectious hepatitis while in the case of serum hepatitis such a diet appears to be without advantage and may actually be deleterious in some situations.

These measures of control and management are illustrated from the results of a series of studies conducted in human volunteers which had as their purpose the evaluation of the safety of blood and blood products with respect to serum hepatitis.

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LOW RESISTANCE TO INFECTION: RELATIONSHIP TO ABNORMALITIES IN GAMMA GLOBULIN*

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I WOULD like to take a moment to review briefly what is meant by the term "γ-globulin." As we all know, the γ-globulins are a group of proteins present in normal human plasma with which are associated the antibody properties of blood. With the role γ-globulin plays and may play in modern medicine, it is somewhat disillusioning to note that the term γ-globulin was applied to this group of plasma proteins simply because it was the slowest of three main groups of globulins migrating in an electrical field and what could be more logical than simply designating it by "γ", the third letter of the Greek alphabet? Through the ingenuity and perseverance of Dr. E. J. Cohn and his collaborators, it was found possible to chemically isolate the γ-globulins from pooled normal human plasma and subsequent investigation has revealed that almost all the antibodies of human blood are in this γ-globulin fraction. It is at once apparent, therefore, that low resistance to infection would be one of the most probable consequences of a deficiency or absence of this group of proteins in an individual.

This evening, I should like to discuss several clinical conditions in which a marked deficiency or even absence of γ-globulin does indeed occur in association with severe recurrent bacterial infections. Since such a deficiency may result either from failure in formation of γ-globulin or from excessive loss of γ-globulin from the circulation, these conditions may be divided into a primary group and a secondary group. In the primary group, the marked deficiency or absence of γ-globulin is due to a failure in the *synthesis* or formation of γ-globulin, whereas

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in the secondary group, the deficiency is due to excessive catabolism of γ-globulin or to direct loss of γ-globulin from the circulation. The primary group may be tentatively subdivided into at least three clinical forms of hypogammaglobulinemia: 1) congenital agammaglobulinemia, 2) adult agammaglobulinemia, and 3) transient or physiological hypogammaglobulinemia. The secondary group is even less clearly defined but an example of this group would be the nephrotic syndrome in children.

With Dr. Charles A. Janeway, Dr. Leonard Apt, Dr. John Craig and with the help of our colleagues at other institutions, it has been our privilege to observe and study fifteen children with congenital agammaglobulinemia. Of these fifteen patients, all have been males; in three instances there has been a history of other male members of the immediate family having died of presumably the same condition, and, in three families, maternal uncles or maternal male cousins were similarly afflicted. In one case, three male siblings succumbed to bacterial infection, and the only female escaped unscathed—and this in the last ten years during the age of antibiotics. These findings plus the fact that this condition is first manifested in infancy or very early childhood have suggested to us that it is probably congenital and that the defect is presumably hereditary, being recessive and sex linked, the inheritance pattern resembling that for hemophilia. As a word of caution, may I remind you that, with this type of inheritance pattern, it is at the moment theoretically possible, although unlikely, that a female may have this condition.

Clinically, these children when untreated are characterized by an unusual frequency of severe bacterial infection.[1-3] Pneumonia, septicemia and even meningitis are of relatively common occurrence in this group of patients. The individual picture, however, is by no means constant. One patient may be afflicted with repeated attacks of pneumonia; another may suffer several attacks of meningitis alternating with episodes of pneumonia or septicemia; while still another patient may have persistent sinusitis and otitis media eventually culminating in meningitis. Thus, the pattern of infections encountered varies considerably from patient to patient. While congenital agammaglobulinemia would be an obvious possible diagnosis in the child with recurring severe infections, it might not be so apparent in a patient with a milder course. Our awareness of this condition is increasing as our experience grows; as an ex-

ample, a random sampling in a small bronchiectasis clinic revealed two children with agammaglobulinemia. Since available prophylactic therapy has proven quite effective, early recognition of this condition is essential *before* irreversible structural damage to organs occurs, *before* the child develops irreversible bronchiectasis as a consequence of bronchopneumonia, or cerebral palsy and mental retardation as a result of meningitis.

In view of the severity and frequency of the infections endured, it is doubtful that many of these children would have survived before the days of chemotherapy. Although these children are extremely susceptible, and several have succumbed, to multiple recurring bacterial infections, their response to some of the viral infections of childhood has been relatively normal. In accord with this finding is the fact that although these children failed to produce detectable antibodies in response to artificial stimulation with a variety of bacterial antigens, vaccination with vaccinia virus resulted initially in normal primary takes followed by an immune response to vaccination two to three weeks later. Antibodies against vaccinia virus were either absent, however, or present in very low titer even after three or four vaccinations in the same individual in different sites at different times. And interestingly enough, vaccination six months after two preceding vaccinations in two individuals resulted in an accelerated type of reaction followed by immune reactions. Thus, human immunity against vaccinia virus may depend upon a change in host cells as well as upon circulating antibodies.[4] In addition, for some viruses very little antibody may be required for immunity; the classic example is the use of very small doses of γ-globulin derived from *normal*, not convalescent, plasma for passive protection against measles.

In studying the antibody responses of these children, it was also found that these patients lacked isohemagglutinins in their sera, irrespective of their blood groups. In fact, in an early stage of our investigation the presence or absence of isohemagglutinins was used as a simple laboratory screening test for this condition in patients of blood groups O, A or B. Obviously, it could not be used for patients of type AB.

Although all of these patients failed to show γ-globulin upon electrophoretic analysis of their plasmas, more sensitive immunochemical analyses show that very small amounts of γ-globulin, less than 30 mg. per cent, may be present in some of these patients; the level of most of the

patients, however, has ranged from 4 to 18 mg. per cent. The normal concentration of γ-globulin in plasma is about 10 to 15 per cent of the plasma proteins or about 600 to 1200 mg. per cent. The quantitative immunochemical procedure proved far more reliable and accurate than electrophoresis for the diagnosis of this condition. A simple procedure was developed using horse antiserum against human γ-globulin incorporated in agar and placed in a long thin tube. The serum of the patient is simply placed over the antiserum-agar in the tube and the tube allowed to remain at room temperature for eighteen to twenty-four hours; sterile conditions are not observed. The presence of a band of precipitate in the agar indicates the presence of γ-globulin in the patient's serum and the distance the precipitation band has migrated away from the interface between the agar and patient's serum indicates the concentration of γ-globulin.[5]

We have been able to demonstrate that the marked deficit or absence of γ-globulin in these patients is in fact due to a failure in the formation or synthesis of γ-globulin and cannot be attributed to an increased rate of destruction of γ-globulin. Gamma globulin administered to these patients, whether intravenously or intramuscularly, is metabolized at a normal or even slower than normal rate and hence the deficiency could arise only as a result of failure of synthesis.[2]

The failure of synthesis of γ-globulin has also been demonstrated on a cellular level as well.[6] The histopathology of this condition is characterized by a marked deficiency or absence of those cells presumed to be the source of antibody, the plasma cells. In the normal child, antigenic stimulation of a lymph node results in the appearance of plasma cells containing antibody specific for the stimulating antigens. Such cells are not found in the stimulated lymph nodes from children with agammaglobulinemia. In fact, while gamma globulin was readily demonstrated in the blood vessels, lymph nodes and connective tissues of normal children,[7] it was not detectable in the tissues of children with this disease. More conventional examination of the tissues of these patients revealed a marked diminution of lymphoid elements with complete absence of plasma cells from sites where they would ordinarily be found, such as in the lymph node, spleen, and intestinal wall.

The antibiotics, although useful in controlling an immediate infection in these children, have been only partially successful in prophylaxis. On the other hand, γ-globulin administered intramuscularly, 0.1 to 0.15

grams or 0.6 to 1.0 cc. per kilogram of body weight once a month, has given these children considerable protection. Conversely, in the control of an infection, the antibiotics have been more useful than gamma globulin alone.

This then constitutes the syndrome we have chosen to call congenital agammaglobulinemia.

There is another form of agammaglobulinemia which is manifested in adults.[3] Adult agammaglobulinemia is similar in many respects to that seen in children. It differs from the disease in children in that: 1) The concentration of plasma γ-globulin has tended to be a bit higher in those patients studied, with a range from zero to 100 mg. per cent. 2) Either males or females may be affected. 3) The disease did not become manifest until adulthood, the age range being seventeen to seventy-one years of age; in one case of agammaglobulinemia occurring in a female, however, recurring infections began at seven years of age. Adult agammaglobulinemia may be an acquired disease, but it is, of course, possible that this form also is inherited and does not become manifest until adulthood.

There is one form of hypogammaglobulinemia that occurs in infants as a variant of a normal physiologic process. The γ-globulin possessed by the newborn infant has apparently been obtained from the maternal circulation; adequate synthesis of γ-globulin by the infant, however, ordinarily does not occur until the infant is between four to twelve weeks of age. Thus, the γ-globulin level in the infant slowly declines as the γ-globulin of maternal origin is metabolized and the level reaches its lowest point between four and twelve weeks of age.[8] Then the amount synthesized by the infant exceeds the amount destroyed and the level of γ-globulin slowly rises. In several patients, the low level reached has been in the hypogammaglobulinemia range; the lowest level we have observed, however, was 75 mg. per cent. Because the hypogammaglobulinemia is transient and lasts but for a short period as a rule, the patient usually encounters no difficulty. Rarely the hypogammaglobulinemic state has persisted several months with associated recurrent severe infection. The existence of such a state makes a definite diagnosis of congenital agammaglobulinemia very difficult in a patient under six months of age unless the patient is followed very carefully.

In classifying hypogammaglobulinemia, or deficiency in circulating γ-globulins, we described a secondary group and mentioned nephrosis

as an example. In nephrosis, there is persistent severe loss of γ-globulin from the circulation through the renal glomerulus, resulting in serum γ-globulin levels averaging about 200 mg. per cent. In the edema and ascitic fluids of these patients, the concentration of γ-globulin is exceedingly low, the averages being 2 and 10 mg. per cent, respectively. Comparable body fluids in the normal child would contain about 200 to 300 mg. per cent. Thus the ascitic fluid from nephrotic patients could serve and has served as a culture medium. However, factors other than diminished γ-globulins in the nephrotic syndrome may be related to the low resistance to infection exhibited by these patients and the γ-globulin picture may not be the whole story.

It must be remembered that the term γ-globulin is not synonymous with antibody since it is the individual specific groups of antibodies that as a whole comprise part of the γ-globulin fraction. It is probable that proteins other than antibodies, whose functions are at the moment obscure, constitute some fraction of γ-globulin. And to further compound the complexity, antibodies have been found in other protein fractions such as α and β globulins, although even when in these fractions they appear to be immunochemically related to the γ-globulins. Hence, it may be entirely possible to have low resistance to infections or low resistance to a group of organisms through: 1) an error in the metabolism of a specific group of antibodies; 2) deficient or even defective formation of antibodies in general either with a) normal synthesis of other γ-globulins or with b) abnormal synthesis of γ-globulin. Thus, it might well be possible to have a condition of low resistance to infections with normal or even elevated concentrations of γ-globulin in the circulation. Cases which may fall into such a group have been observed.[9] These clinical states, however, must await further investigations.

Although this evening we have discussed γ-globulin in relation to low resistance to infection, when confronted with the patient subject to recurring infections it is imperative to remember that there are many factors in natural resistance other than antibodies: to mention a few—lysozyme, the phagocytic system and complement.

And finally, while such studies in modern medicine have become more and more complex, paradoxically they have served to simplify the diagnosis and treatment of our patients.

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THE MANAGEMENT OF CEREBRAL ARTERIOSCLEROSIS: PSYCHIATRIC ASPECTS*

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MANY investigators believe that the etiology of cerebral arteriosclerosis remains speculative, but comparatively recent psychiatric studies suggest that heredity and tension contribute at least some influence in its causation. Little has been done to correlate personality studies with organic disease. However, many inferences and unsubstantiated concepts have been proved erroneous by the reports of Gellerstedt[1] and others that comparatively advanced changes, particularly of the type found in the senile psychoses, can also be demonstrated in the brains of well adjusted old persons. With this as a starting point, a new conception of senile and arteriosclerotic psychoses was advanced when recent researches on these disorders by Rothschild and Sharp[2-6] revealed a frequent lack of correlation between the severity of the mental disturbances and the extent of the cerebral damage. These observations suggested that cerebral alterations might not be the only etiological factor in senile and arteriosclerotic psychoses but that psychologic factors might exert an influence on their origin. In certain cases worry, anxiety over failure of health with advancing years, financial hardships, loss of relatives, personality defects and the like seemed worthy of attention. It is important to study these aging patients as persons who break down because of two complementary sets of factors—personality problems and degeneration of brain tissues.

In a clinical approach to the understanding of cerebral arteriosclerosis we must first try to distinguish between cases with and without psychoses and also between the psychoses with cerebral arteriosclerosis and the senile psychoses. These conditions merge into each other, and sharp differentiations are frequently impossible. The functional element is significant in the establishment of a favorable prognosis. Often the

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symptoms in and of themselves are pathognomonic of no one clinical entity. It is the way they are grouped into syndromes, the timing of their onset, and the rapidity of evolution of their development that are important.

First let us consider the cerebral arteriosclerotic without psychosis and with no evidence of even a transient episode of thrombosis of a small intracranial artery. These patients do, however, offer clinical evidence of a slow, gradual diminution of the blood supply of the brain. The first manifestations are likely to occur sometime after the age of fifty following a sudden change or even an anticipated change in their accustomed pattern of daily activity. The first symptom is usually fatigue and an associated loss of interest before or shortly after retirement from business or profession. It may follow moving into a different locality or the loss of a loved one, money, social or professional prestige. Powers of prolonged concentration diminish, especially in any new activity. Another common symptom is normal activity in the forenoon and dozing in the afternoon or early evening in a person who formerly had been alert and interested throughout the day. Such persons have a remarkable ability to awake at the slightest stimulus, to be immediately alert, to infer accurately what has transpired while they were asleep and to continue as efficiently as before. The placid can usually control their irritability, but the more dynamic are given to sudden explosive outbursts of anger, only to apologize immediately after. They are aware that something is wrong but loath to mention it to others. Often they are silent worriers with one-track minds that have made them successful in chosen professions, but without inner resources or an avocation. They may still function in advisory capacities, make out their income tax forms or even drive an automobile across the continent. They may gradually develop more objective symptoms or suddenly die of cerebrovascular hemorrhage.

Among those with more advanced cerebrovascular disease, we have the group subject to what Alvarez[7] calls "the little strokes." This group is apt to be intermittently psychotic in a manner obvious to a careful observer. They spend ten to twenty years dying, gradually fading out with cerebral arteriosclerosis and occasional episodes of thrombosis of a small intracranial artery. These episodes are seldom recognized as manifestations of a long-lasting, eventually fatal disease. Because of its chronicity the course of the illness can be observed adequately only

by the victim's relatives or long-time friends. The first episode may come in the forties or even in the thirties; it frequently occurs unobserved during sleep. A sudden change in character and ability makes the diagnosis relatively easy, although these manifestations may be interpreted as an unexplained nervous breakdown. A psychologic disorder may develop, characterized by moral deterioration, indifference to personal appearance, undue emotional lability or a state of agitated depression, making the patient a difficult problem in the home. A fall, attributed to tripping, may be due to a momentary loss of consciousness. Cerebral disease may cause them suddenly to be unable to sleep.

The subjective symptoms are eventually, either slowly or suddenly, augmented by neurologic signs. Many patients suffer with sudden distress in the thorax or abdomen often attributed to "acute indigestion" but apparently referred from the brain. Indigestion due to muscular spasticity of the digestive tract may ensue. Vertigo is common. The clinician should watch for a slight bulbar paralysis, a Parkinson syndrome or paresthesias and numbness, as well as a slight weakness of muscles, significant loss of weight, a burning sensation or a bad taste in the mouth, a facial pain, sudden blindness or arthritis in a weakened extremity. Frequently a marked drop in blood pressure occurs immediately after one of the small thrombotic cerebral traumas.

The prognosis is often better than might at first be expected. Patients may live for years without another episode and may even continue some form of remunerative employment. These patients require careful observation because of their tendency to be intermittently psychotic. Under stress or strain they tend to become confused, irritable, even delusional and show poor judgment. They frequently display diurnal variations of insight and judgment according to the efficiency of the cerebral vascular structures and the resultant amount of blood supplied to the brain at the moment. They may be lucid and aware of their environment at one hour of the day and confused, delusional, suspicious and even paranoid the next. Allen and Clow[8] have pointed out that it requires judgment and insight based on years of experience to determine their legal and social status in the community and also whether they are capable of understanding the nature of a business transaction or making a valid signature. In such matters psychiatric help is advisable. Frequently paranoid trends are associated with organic brain disease; in the arteriosclerotic patient the cause is often not recog-

nized until after the patient's accusations have received credence and unfortunate situations have occurred.

The organic impairment often releases the control that is exerted over latent sexual urges when the brain is functioning adequately. Such patients are often accused, doubtless in some cases justifiably, of corrupting the morals of minors, but remember it may be the youth who exploits the aged person. The cerebral arteriosclerotic patient may also be induced to make a disastrous marriage with an unscrupulous, usually younger, member of the opposite sex. This frequently results in prolonged litigation over matters of inheritance.

Doty[9] has differentiated the physiologic and psychotic factors that predispose the older person to delirium. Patients whose basic personalities have shown such features as sensitiveness and a tendency to suspiciousness and jealousy may display prominent delusions of persecution during a delirium and may only partially recover from this acute mental disturbance. Prolonged recumbency, contributing to circulatory stasis, is an important factor in any delirium. Perception is not as prompt and its span is not as long as in the young, facts that may contribute to a tendency to misinterpret environmental stimuli so that visual and auditory illusions develop more readily. Doty advocates the early recognition of a developing delirium in order that sedatives or other drugs that may be responsible may be discontinued. Hydrotherapeutic measures or other non-drug methods of securing rest and sleep for the patient should be instituted. Treatment to promote excretion of drugs and waste products through the skin, kidneys, and bowels should be prompt. Avoid confusing or puzzling treatments and explain all necessary ones. Also, reduce all possible external stimuli by refraining from changing the patient's location and having as few physicians and nurses caring for him as possible. Exclude all visitors and keep him under constant observation. Proper nursing supervision is the most important of all. With the prompt withdrawal of sedatives, with proper fluid and nutritional intake and adequate elimination, the delirium usually subsides in a period of a few days to several weeks with a return to as great a state of efficiency as before. Sands[10] in a study of cases of cerebral arteriosclerosis with confusion due to infection, found that with proper treatment of the infection, recovery from the confusion occurred within one to three months.

The symptoms of a psychosis associated with cerebral arteriosclero-

sis have been enumerated in greater detail by Rothschild[11] than by other investigators and he has differentiated them, as far as it is clinically possible, from the senile psychoses. The emotional picture in cerebral arteriosclerosis is a more varied one than in senile dementia. The physical manifestations are more pronounced. Rothschild also noted periods of loss of consciousness alternating with or followed by periods of amazing lucidity. The process is a more reversible one than that in senility in which the symptoms are associated with a progressive and more or less slow alteration or degeneration in the brain tissues themselves.

In a psychosis associated with cerebral arteriosclerosis there are likely to be prodromal or early symptoms in accordance with a variation in the pressure and alteration in the amount of blood in the cerebral arteries. The most common prodromal symptoms are headaches, dizziness, vague somatic complaints and a more or less prolonged period of physical or mental letdown. Apoplectiform or fainting attacks, symptoms of cardiac decompensation and, less frequently, convulsive seizures often precede the mental symptoms, although these physical phenomena may occur at any time during the course of the disease.

Although the mental symptoms may be sudden or gradual in development, a sudden attack of confusion is noted in more than 50 per cent of the cases; the neurologic symptoms often predominate. The patients show marked clouding of consciousness, complete loss of contact with their surroundings, incoherence and pronounced restlessness. Hallucinations may be added to produce a delirious picture. In some cases there are few, if any, premonitory symptoms, but as a rule the onset is preceded by a gradual reduction of physical and mental capacities.

With this gradual onset the mental disturbances are similar in many respects to those observed in senile dementia. There is a gradual intellectual failing, manifested by a loss of efficiency, and impairment of memory. The patient may become irritable, aggressive and display a lowering of moral standards. Subjective complaints, such as weakness, fatigue, uneasy feelings and unpleasant somatic sensations are frequently noted. Depressive feelings and a fear of impending failure, with physical and mental inadequacies, are often prominent; overt suicidal tendencies are by no means uncommon. Explosive outbursts of weeping or laughter are occasionally encountered, usually in cases with gross neurologic alterations. Transient persecutory ideas or jealousies may be

observed, but persistent well developed paranoid ideas are rarely present. Delusions and apprehensions appear more frequently in the evening, often interfering with sleep. The impairment of memory tends to affect recent, rather than remote, impressions but is apt to be spotty rather than diffuse. Fabrications are sometimes noted. Although judgment is impaired, this seems dependent on the efficiency of the cerebral circulation at the moment. Periods in which even the psychotic cerebral-arteriosclerotic patient may show lucidity and insight should be accurately recorded by competent observers and capitalized upon when it may be expedient for the patient to make a valid signature to a business transaction.

Beckenstein and Gold[12] studied 100 consecutive patients with senile psychoses and 100 consecutive patients with cerebral arteriosclerosis who were admitted to the Brooklyn State Hospital from April to June 1943. The study showed that the total duration of mental illness in the senile psychotic patient tended to be one to three years, and that in the cerebral-arteriosclerotic patient who was psychotic the total duration is generally less than two years. The cerebral-arteriosclerotic psychotic patients had a greater chance of survival; when well enough to leave the hospital they were generally discharged within two months. In the senile psychoses the type of onset was not of much significance, as the disease was progressive and the outcome was the same whether the onset was acute or insidious. The greater frequency of the acute onset among the cerebral-arteriosclerotic group was demonstrated by the fact that 77 per cent had this type of onset, which corresponded with Rothschild's findings and seemed of some value in determining the prognosis.

Clow[13] in 1939 made a detailed study of 100 patients suffering from psychosis with cerebral arteriosclerosis who were treated at The New York Hospital–Westchester Division. Fifty-five of the 100 patients had a family history of cerebral arteriosclerosis as manifested by cerebral accidents. The members of the families were predominantly tense and aggressive. Manic-depressive psychoses were prominent in the family histories. The patients also had frequently had affective psychoses. Many of them suffered from peripheral and retinal arteriosclerosis with hypertension. Fifty had a history of vascular accidents; fifty-nine showed focal signs. Precipitating emotional factors were noted in seventy-six cases, the most common of these being the illness or death of

a close relative or friend. The toxic effect of drugs contributed to the psychotic symptoms in thirty-seven patients. Treatment necessitated a knowledge of both psychiatry and internal medicine. Adequate fluid intake, easily digestible food, enemas, massage, baths, packs and proper rest were helpful at first. These were followed by the stimulation of the interests of the patients and the awakening of new ones. They were encouraged to make friends and to follow a prescribed routine of physical activity and occupational therapy in keeping with their capacities. Reassurance and teaching the patients to be content to live within their limitations were beneficial. It was also equally important to educate the patients' families concerning their condition and how to modify their environment when they returned home.

Under this treatment, eleven of the patients recovered from their psychoses, five with slight residual memory defects. Twelve were much improved, thirty-one were somewhat improved, thirty were unimproved and sixteen died. What is especially significant is that forty-nine of the 100 patients were able to return to their homes. This study strikes an optimistic note by showing that in psychotic patients with cerebral arteriosclerosis a functional reversible element may be present and that under suitable conditions a certain percentage recover.

Subsequent studies by Allen[14] at the New York Hospital–Westchester Division have revealed that a systematized routine, with proper nursing care, adequate nutritional intake and proper elimination frequently conduces to a state of adjustment in which the patient can function comfortably without supportive drugs, sedatives or special diets. Many patients come to the hospital suffering from psychoses with cerebral arteriosclerosis who have been taking barbiturates, aminophylline, paraldehyde and Demerol and have been on low-protein, salt-free diets. Within a few days all these aids can, in most cases, be discontinued.

There are definite reasons for this. When such patients are cared for in their homes or in a general hospital, if they are noisy, they at once attract attention and awaken apprehension. It is often expedient for the welfare of others to quiet them as quickly as possible. At home, the physician rarely visits them oftener than once daily, and the nurse is frequently on twelve or twenty-four hour duty. Sedatives lessen the work of both physician and nurse. In a general hospital both physician and nurse have to meet the criticisms of other patients and relatives. In a mental hospital with adequate personnel, someone is always available

who can talk quietly with the patient and exert a personal influence. In an adequately staffed mental hospital the personnel can relieve one another; hence the physician, nurse or attendant in charge of the patient can approach him fresh and relaxed and thus not unfavorably influence the patient with personal tensions, anxieties or irritations resulting from his own accumulated fatigues. Furthermore the personnel of a mental hospital see and treat such patients constantly and are not merely confronted sporadically with isolated cases; they thus have an assurance and confidence that the patient is quick to appreciate. Having the patient under constant twenty-four hour supervision enables the personnel to ascertain quickly whether their methods are producing a favorable response or not. It takes courage to know when to refrain from prescribing for the patient. Keeping the patient under unobtrusive surveillance is desirable, but we must all at times curb our professionally conditioned impulses constantly to do something for or to the patient.

Sometimes digitalis, Demerol, morphine, aminophylline or paraldehyde is indicated, but such medication should be discontinued as soon as possible. The advisability of medication is checked by continuous clinical observation and by laboratory studies. The orders for any medication are written daily; standing orders, which are likely to be continued for indefinite periods, are prohibited. Special diets are likewise sometimes necessary, but these can be quickly modified with adequate clinical and laboratory supervision.

For elimination, simple cathartics like milk of magnesia or cascara with mineral oil are usually sufficient, but they should also be quickly reduced or used intermittently. The lower bowel is often sluggish and lacking in musculature. The need for enemas should be determined by rectal examination by the physicians rather than by the statements of the patient or the nurses. Usually a low enema once or twice a week, preceded by an oil instillation, is sufficient. Often a clear return from an enema is reported; this may be due to canalization of the fecal material by the enema tube. In a rectal examination carefully palpate the walls of the rectum or descending colon. The depleting trauma of colonic irrigations should be avoided.

In a consideration of electric shock therapy, Prout and Hamilton[15] have pointed out that while it is not indicated as a specific treatment, it is a relatively safe procedure for many complicating emotional disorders of these patients. A careful survey of the adequacy of the cardio-

vascular system is essential. Hypertension, abnormal electrocardiograms, a history of angina pectoris or coronary thrombosis and inactive rheumatic heart disease with valvular lesions are not in themselves contraindications to electric shock therapy. A patient whose cardiac reserve enables him to walk 100 yards without obvious distress is able to stand electric shock treatment. Added assurance is given when the muscular response is modified by a curare derivative. The patient should first have the opportunity to respond adequately to the more conservative methods of psychiatric therapy, but agitation and excitement may put more strain on the heart than the electrically induced convulsion.

The use of a curare derivative prior to electric shock treatment, when carefully administered by trained and experienced physicians, is a safe procedure with the cerebral-arteriosclerotic patient who has no gross neurologic symptoms or history of recent cerebral thrombosis or hemorrhage and whose electroencephalogram reveals no evidence of serious brain disease. The curare derivative can be safely given in such doses as are necessary to prevent any true convulsive reaction (clonic or tonic muscular responses), allowing only isolated fibrillary twitchings that are not capable of changing the position of the extremities. Adequate resuscitative equipment should be always immediately available.

When nonpsychotic and not too severely physically handicapped the cerebral arteriosclerotic should be kept employed. The greatest obstacle in effecting this is a sense of fatigue and lack of interest. Many patients may recover some degree of functional efficiency and return to their homes. Many are more alert than might appear on superficial observation, are aware they are inadequate but preserve some degree of intellectual integrity. Knowledge of these facts will not only prolong their lives but will make them more comfortable and give the physician the satisfaction of knowing that he has restored some of them to a degree of usefulness in their community.

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RETINAL AND CONJUNCTIVAL VASCULAR CHANGES IN NORMAL AND TOXEMIC PREGNANCY*

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ADDITIONAL evidence has now accumulated indicating that there are changes in the peripheral vascular bed, both in normal and toxemic pregnancy.[1, 2] Initial observations of the arterioles in toxemia date back a century. Soon after the discovery of the ophthalmoscope, retinal detachment associated with toxemia,[3] was described in 1856. From 1895 to 1924 various authors reported the presence of retinal hemorrhages and transudates in the toxemias of pregnancy.[4, 5] They were all aware that such findings indicated a poor prognosis for the infant, with a survival rate of approximately 25 per cent. Volhard in 1921[6] was responsible for the theory that these retinal changes resulted from arteriolar spasm which produced areas of ischemia and secondary hemorrhage. Prior to that date, the general impression was that the retinal abnormalities were related to renal disease and associated albuminuria.[7] In 1928 Haselhorst and Mylius[8] clearly recognized the presence of localized and diffuse arteriolar spasm which was reversible in eclampsia. Since that time in this country numerous reports have confirmed the arteriolar changes that occur in toxemia of pregnancy (Mussey and Mundell,[9] Wagener and Keith,[10] and Hallum[11]).

Retinal hemorrhages in vomiting of pregnancy were first discovered by Stander,[12] and Tillman[13] in 1932 and 1934 respectively. A summary of this state by Schjøtt-Rivers[14] indicated the importance of extensive retinal hemorrhage associated with vomiting of pregnancy. Failure to interrupt the pregnancy in many instances resulted in maternal death. At the present time, probably related to improved methods of parenteral feeding, retinal hemorrhages in vomiting of pregnancy are almost un-

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known. Rare fine "splinter" hemorrhages[15] have been noted during a severe episode of vomiting, and then have been seen to disappear after commencement of intravenous feeding.

During normal pregnancy, no observable variations have been seen in retinal arterioles and venules. In mild pre-eclampsia minimal changes or early mild spasm have been noted, whereas in severe pre-eclampsia, more advanced retinal changes occur. Increasing spasm usually is indicative of a further advancement in the toxemic process. However, any reduction in the spasm associated with severe pre-eclampsia does not necessarily mean improvement of the toxemic state. At times, a sudden decrease in arteriolar spasm may suggest early fetal death. Retinal hemorrhages and transudates are extremely rare in acute toxemia. Their presence indicates interruption of pregnancy to preserve maternal vision, and continuation of pregnancy will probably not improve the fetal survival rate. In our experience the presence of retinal hemorrhages in acute toxemia is associated with a 33 per cent fetal mortality rate. The early onset of eclampsia is usually concomitant with the more advanced retinal findings. Acute eclampsia in the final weeks of pregnancy is generally associated with severe reversible arteriolar spasm. In this late type of eclampsia, there is ordinarily no silver wire appearance or evidence of arteriovenular compression. The presence of a hydatidiform mole in the second trimester of pregnancy is on occasion associated with advanced arteriolar spasm. Such vascular phenomenon in the second trimester, unassociated with known hypertensive disease, suggests the presence of a mole.

Ophthalmoscopy is most useful in the diagnosis of severe essential hypertension.[16] Evaluation of essential hypertension prior to, or early in pregnancy, to determine the chances of a successful outcome, should always include bilateral retinal observations. The presence of Grade II spasm, old hemorrhages, transudates, and silver wiring of the vessels indicates a poor prognosis for a living infant. If retinal hemorrhages are evident, pregnancy is contraindicated and therapeutic abortion should be performed.

In benign hypertension with a blood pressure elevation at moderate levels (diastolic pressure of 90 to 109), minimal retinal arteriolar changes may be observed. If superimposition of toxemia does not occur, retinal observations are only of use as a baseline for the evaluation of later changes. In severe hypertension, in which the diastolic pressure is above

* Fig. 1—M.S. shows marked local arteriolar spasm (arrow) and Grade II changes (three weeks before delivery).

110 mm. Hg, the retinal arterioles contribute important information for fetal prognosis, and may indicate further exacerbation of the toxemic process. If albuminuria and severe hypertension are associated with Grade II retinal arteriolar changes (severe local and generalized spasm), fetal growth usually ceases and intrauterine death may be anticipated in an average of three weeks after the onset of superimposition.

Case 1. M.S. (No. 197999), a forty-one-year-old para 0, gravida ii, was admitted in 1948 because of an increase in hypertension to 170/110 during the twenty-ninth week of pregnancy. A previous pregnancy

* Figures 1, 2 and 3 are from Landesman, R. et al.[18] in American Journal of Obstetrics and Gynecology, 63:16-27, 1952. Reprinted by permission of the publisher, C. V. Mosby Co.

had terminated spontaneously at the twentieth week. No albuminuria or edema was present. Retinal vessels of Grade II, with severe local spasm and arteriovenous compression phenomena, were observed. By the thirty-third week the blood pressure had returned to the previously recorded mild hypertensive limits and the spasm in the eyes was noted to be decreased. However, the fetal heart was absent ar[illegible] one week later a 1330 gm. macerated infant was delivered. Renal function and blood uric acid levels were within normal limits. The blood pressure decreased to 140/90 and retinal spasm subsided one week prior to delivery, which was probably the time of fetal death. Nine months postpartum blood pressure was 180/120 without clinical symptoms. Figure 1 shows the Grade II retinal arteriolar spasm. The exacerbation of blood pressure in the twenty-ninth week of pregnancy and Grade II retinal changes were followed rapidly by fetal death. The improvement in the retinal vascular picture with an associated drop in blood pressure occurred soon after the infant's death. These ophthalmological observations of the retina, as well as those of the other cases presented, have been made by a member of the Ophthalmology Department of Cornell University Medical College. The accuracy of classification of retinal findings improves when only one examiner is responsible for all the observations. Similar experience has been noted by Dieckmann.[17]

The presence of Grade III changes in the retinal vessels associated with essential hypertension is a serious complication in patients whom we have followed. Hemorrhages and transudates associated with essential hypertension usually result in a 75 per cent infant mortality. It is common, following the interruption of such a pregnancy, for most of the hemorrhages and transudates to disappear spontaneously with the subsidence of the toxemic process.

Case 2. E.F. (No. 137025), a forty-two-year-old para viii, gravida xii, with seven living children, was admitted in the thirty-fourth week of pregnancy because of hypertension (170/105). She was first seen in 1936 for severe pre-eclampsia complicated by premature separation of the placenta, and she subsequently delivered a stillborn infant of 3830 gm. In 1940 a pregnancy was again complicated by severe hypertension, the blood pressure reaching a level of 180/120. Following a term delivery the blood pressure was 145/115. The patient was advised against future pregnancies and a tubal sterilization was suggested, but she refused. She was seen during the present pregnancy on the day prior to

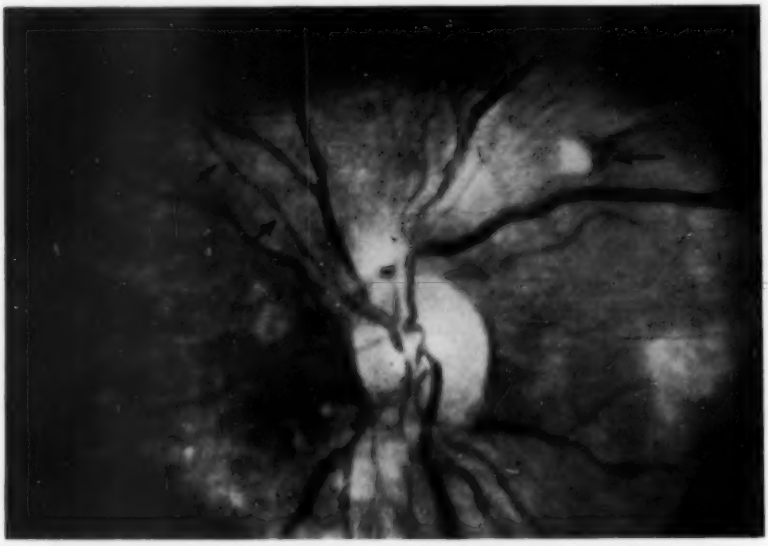

Fig. 2—E.F. shows Grade III changes with local spasm, hemorrhages, and transudates. Carbon arc spot adjoins disc at 11:30 (sixteen hours before cesarean section).

admission, when the urine showed a 4 plus albumin. The eye grounds showed copper and silver wire arterioles with local and generalized spasm and transudates, and were classified as Grade III (Fig. 2). A low flap cesarean section and tubal sterilization were performed and a healthy 2820 gm. infant was delivered. Blood pressure at the time of section was 190/120 and ten days postpartum it was 165/100. The final diagnosis was severe hypertension with superimposed pre-eclampsia. There was some reduction of renal function postpartum. It was fortunate in this case to obtain a living infant.

The baby of the diabetic mother is in general larger than the average.[18] However, when diabetic retinopathy occurs, a normal or smaller than average size infant is the rule. Diabetic retinopathy[19] is characterized in general by small yellowish transudates and deep hemorrhages in the macula area, and small superficial hemorrhages around the disc. The following case illustrates this process.

Case 3. J.L. (No. 550616), a twenty-one-year-old para 0, gravida ii, with diabetes of fifteen years duration, was admitted to the hospital

Fig. 3—J.L. shows mixed diabetic retinopathy (arrow) in the left macular area. Carbon arc spot is above macula. Arterioles show only Grade I changes (five days before delivery).

in 1949 when twenty-four weeks pregnant, because of diabetic retinopathy (transudate and hemorrhages). The blood pressure was 140/90, there was a 3 plus albuminuria, and renal function tests showed a significant impairment. Because of her extreme desire for the infant, the pregnancy was not interrupted. Daily requirements of insulin consisted of 50 units. In the thirty-third week, because of increased generalized edema, excessive weight gain, and progressive retinopathy, a cesarean section was performed. The infant weighed 1490 mg. and died twenty-four hours later. Postmortem examination showed nothing significant except immaturity. Figure 3 illustrates the diabetic retinopathy with perimacular transudates and hemorrhages.

The early onset of diabetic retinopathy with extension during pregnancy will usually result in multiple scotomata and reduction in vision. If this diabetic retinopathy is extensive in early pregnancy, prognosis for a live infant is usually hopeless. After pregnancy, diabetic retino-

pathy tends to subside and may completely disappear. If, however, the process is extensive, permanent loss of vision may result.

Careful observation of diabetic pregnant women without toxemia has demonstrated no significant changes in the conjunctival vascular bed. This is at variance to a recent report by Ditzel and Sagild[20] who show numerous forms of conjunctival changes. In diabetes associated with toxemia of pregnancy, the conjunctival vessels show similar findings as in other patients with toxemia. Any minor variations in the diabetic are of more significance with the known higher fetal mortality rate in toxemia.

If chronic nephritis is associated with retinal arteriolar changes, the prognosis for a living infant is poor. On the other hand, if albuminuria is present with good renal function and normal retinal vessels, the outlook for a live infant is good. When extensive renal disease is evident, essential hypertension is almost invariably associated with marked retinal arteriolar variations of Grade II or more. This combination should contraindicate pregnancy because of the hopeless prognosis for a live infant and the usually short duration of maternal life. If the diagnosis of renal disease is made late in pregnancy the absence of retinal abnormalities is a good sign for the infant, whereas extensive retinal involvement will usually be associated with reduced fetal growth and intrauterine death.

In view of recent pathological evidence furnished by Hertig,[21] Sheehan,[22] and Falkiner,[23] that toxemias of pregnancy are associated with lesions of the smaller arterioles, it was considered important to observe the peripheral vascular bed in vivo. Observations of finer vessels of the nail bed have been described by several investigators.[24, 25] These vessels, however, appear to represent arteriovenous shunts[26] and are not typical, anatomically, of the peripheral vascular bed. Photographs of these vessels have been unsatisfactory. Following the fundamental work of Lee and Holze[27] on the bulbar conjunctival vessels, a series of normal and toxemic pregnancies was observed, and representative photographs of the vessels were taken by means of a slit-lamp microscope and an attached 35 mm. camera. In normal pregnancy, there are gradual changes in the vascular pattern and in the characteristics of flow. In the first trimester, the arteriolar flow is very rapid, the venules are filled, and the capillary bed is clearly visualized. After the twentieth week, there is a gradual reduction in the rate of blood flow. This slow-

ing appears maximum several weeks before labor, during labor, and in the first three days postpartum. Concomitantly with the reduction in the flow rate, there is the appearance of granularity in the venules which was formerly described as sludge by Knisely and his coworkers.[28] This granularity reaches a peak at about the same time that the reduction in flow rate is at a maximum. We believe that this granularity is directly associated with the rate of blood flow and is not related to the cohesion of red blood cells. Changes in plasma protein,[29, 30] manifested by an increase in globulin and a reduction in albumin, may be partly responsible for the granular appearance. Granularity may be very extensive at the time of labor and so far as we could determine, is a normal variant in pregnancy. Ischemia of the capillary bed is an important alteration in the vessel pattern seen during pregnancy. As term is approached, the number of capillaries visualized gradually becomes reduced; this may be seen without the microscope, by directly observing the bulbar conjunctiva late in pregnancy. In toxemia this ischemia is more prominent. In severe pre-eclampsia and eclampsia, localized areas of the capillary bed in the bulbar conjunctiva for all practical purposes, may be completely absent. This phenomenon is clearly illustrated in the following case.

Case 4. U.A. (No. 664007). This eighteen-year-old primigravida was admitted to the hospital in the thirty-eighth week of pregnancy because of sudden elevation in blood pressure to 150/110, 4 plus albuminuria, and severe headache. On the day following admission the blood pressure rose to 190/120. The membranes were ruptured and during pitocin induction a generalized convulsion occurred. Several hours later a normal healthy 2340 gm. infant was delivered. Two other convulsions occurred immediately following the delivery. At this time, retinal vessels demonstrated a Grade I plus change with mild peripheral attenuation. Conjunctival observations indicated a complete absence of any functioning capillaries. On the sixth postpartum day, the arterioles showed incomplete filling, indicating spasm and profound ischemia of the capillary bed (Fig. 4). Eight days postpartum there was no retinal spasm remaining, and the peripheral attenuation disappeared. At two months postpartum there was a return to a normal conjunctival pattern (Fig. 5).

In the first six months of normal pregnancy, there is no evident arteriolar spasm in the conjunctival vessels. Vasomotion, which is a fine

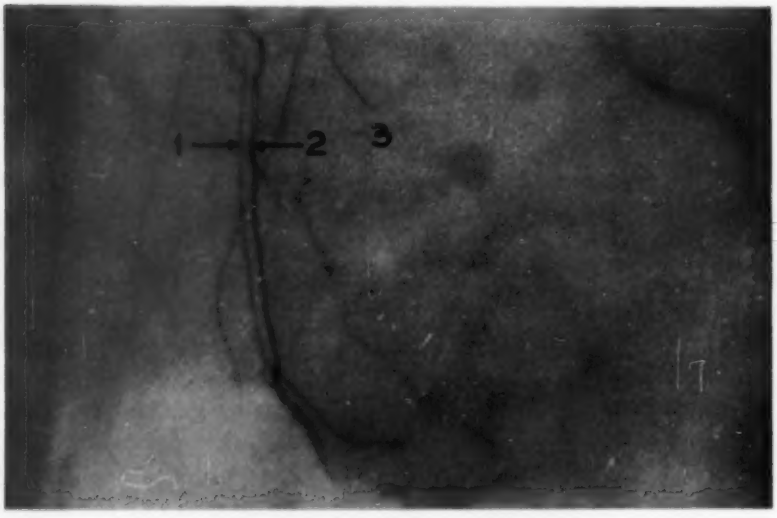

Fig. 4—U.A. Eclampsia. Six days postpartum.
1—Arteriole—Grade II spasm
2—Venule
3—Capillary bed—Grade III ischemia

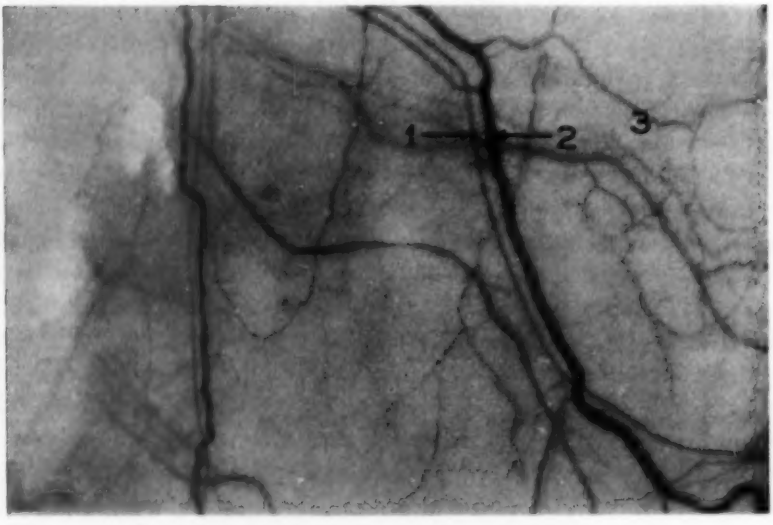

Fig. 5—U.A. Eclampsia. Two months postpartum.
1—Arteriole—Grade 0-1 spasm
2—Venule
3—Capillary bed—normal

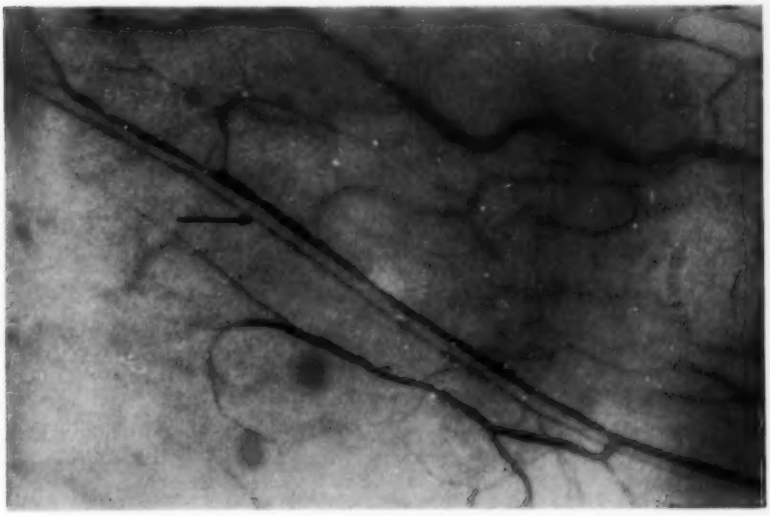

Fig. 6—S.R. 489005. Severe pre-eclampsia. One week prior to fetal death in utero. Grade II spasm.

wave-like activity, may be seen in these vessels. In 20 per cent of the normal, a mild spasm may be noted in the last trimester, during labor, and in the first week postpartum. Any further spasm, Grade II or over, indicates an abnormal process, and is associated with the toxemias. The period of pregnancy, in which the spasm is first noted, may be significant. The presence of moderate spasm in the first trimester is indicative of hypertensive disease, whereas, if it is seen during the course of labor, it may be a part of the normal process. The presence of ischemia is related to the extent of the spasm. In toxemias that occur late in pregnancy, the arterioles become extremely attenuated and are thinned out due to generalized hypertonicity of the vessel wall. Bulbs and areas of spasm are not discernible because of incomplete filling of the vessels. In instances of eclampsia, areas of the conjunctiva show complete blanching with only occasional venules being present. In the following case extensive localized spasm is illustrated in severe pre-eclampsia (Fig. 6).

Case 5. S.R. (No. 489005). This thirty-two year old para iv gravida iv was admitted in the thirty-first week of pregnancy with severe

pre-eclampsia, elevated blood pressure of 150/105, and 4 plus albuminuria. Retinal and conjunctival vessels showed a Grade II arteriolar spasm. In the thirty-sixth week pitocin induction was used to efface the cervix. During the third day of pitocin induction fetal distress was noted and a fetal heart rate of 80 was recorded. When the pitocin was discontinued, the fetal heart returned to normal. Later the same day, because of the small size of the fetus, pitocin was readministered and the fetal heart was lost. The patient delivered a 1410 gm. deadborn in the thirty-seventh week of pregnancy. Urea clearance, blood area nitrogen, and concentration tests were normal.

Tortuosity of the capillary bed is not influenced by normal pregnancy. In approximately 30 per cent of the more advanced instances of essential hypertension, extensive corkscrew-like elongations of the capillaries have been observed. It is our impression that this finding usually indicates vascular disease. In one hundred normal patients studied during pregnancy, extensive tortuosity as described above was not present.

Case 6. H.K. (No. 595414). This twenty-four year old primigravida suddenly developed convulsions in the twenty-seventh week of pregnancy. Prior to this date blood pressure, urinalysis, and weight gain were within normal limits. After three convulsions she was admitted to the hospital. The blood pressure at this time was 174/112, albuminuria was 4 plus, and there was generalized edema. She was given intravenous pentothal and was fully digitalized. Chemical examination of the blood showed a uric acid of 5.0 mg. per cent, total proteins 4.6, albumin 3.7, globulin 1.1 and urinary non-protein nitrogen 34.0. Urinary output was adequate. Ophthalmoscopy showed several areas of moderate local spasm and generalized mild spasm. No hemorrhages or exudates were visualized and the diagnosis was Grade II arteriolar change.

No further convulsions occurred, and the blood pressure receded to border-line levels. However, there were occasional severe frontal headaches and albuminuria persisted, ranging from 3.0 to 8.0 gm. per liter. Frequent measurements of the uterine fundus over a six weeks' period revealed no growth. Retinal observations showed some improvement in the spasm, body edema disappeared, and weight remained stationary. Five weeks after admission, in the thirty-second week, the fetal heart was lost, and one week later a 1000 gm. deadborn infant was delivered. The urea clearance and concentration tests were normal. After ten days

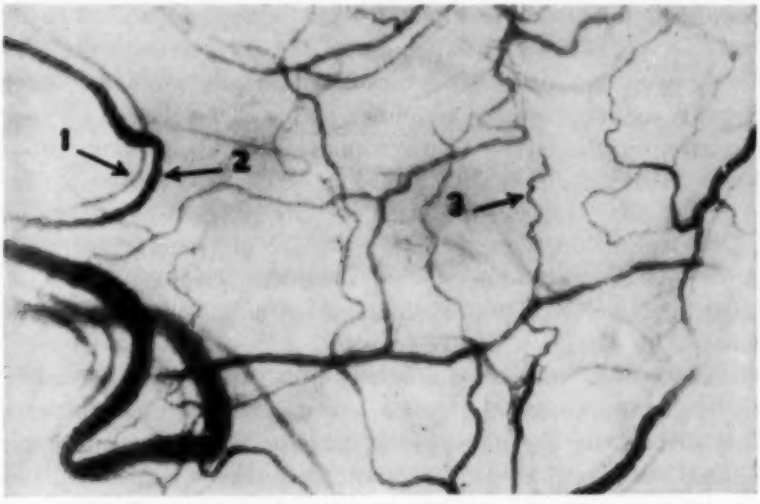

Fig. 7—H.K. Eclampsia. Postpartum. Grade III tortuosity.
1—Arteriole 2—Venule 3—Capillary

(From Landesman, R. et al.[3] in American Journal of Obstetrics and Gynecology, *68*:170-82, 1954. Reprinted by permission of the publisher, C. V. Mosby Co.)

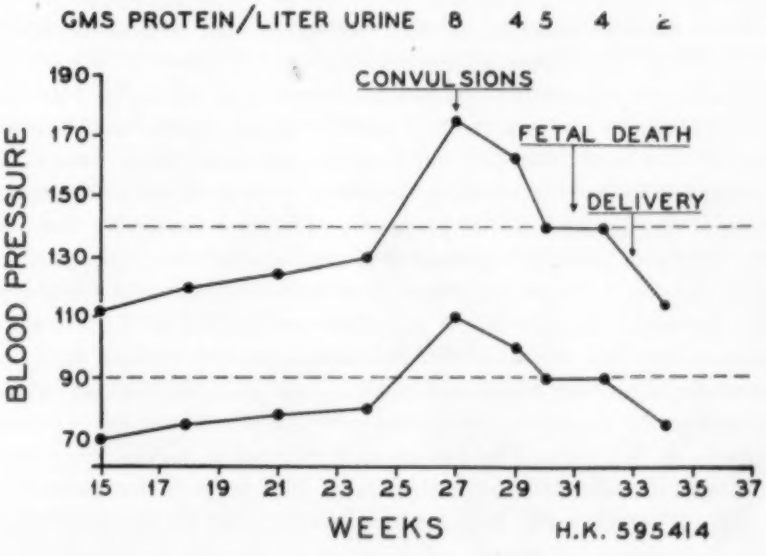

Chart 1

postpartum the blood pressure and retinal alterations returned to normal (Fig. 7). Following this pregnancy she was observed for approximately two years during which time blood pressure was within normal range. A second pregnancy two years later was complicated by severe pre-eclampsia; hospitalization was required and a living infant resulted. Chart 1 shows the clinical course, onset of convulsions, and the time of fetal death. Although the blood pressure returned to normal, and there was some improvement in both retinal and conjunctival vessels, intrauterine death occurred six weeks following the convulsions. In spite of some general improvement, continuation of the toxemic state was indicated by the lack of uterine growth.

Certain other unusual features have been observed in the study of the conjunctival vascular bed in toxemia, which are further evidence of peripheral vascular alterations. In two instances of severe essential hypertension, aneurysmal dilatations of the deep scleral veins have been noted. In four cases thrombi have been seen in acute toxemia and have faded in the first week postpartum. In five patients true conjunctival petechial hemorrhages have been visualized.

Summary

Page,[30] in his recent monograph on the toxemias of pregnancy, indidicates the importance of the arteriolar spasm associated with this disease. Irving[31] and Eastman[32] related some years ago the evidence for the presence of this vascular phenomenon associated with the toxemias. McCall[33] in his study of cerebral circulation, has demonstrated reduced blood flow and increased intravascular resistance in eclampsia. At present, it has not been possible to observe directly the terminal circulation of the placental bed in pregnancy. The total circulating blood to the uterus is probably reduced in acute toxemia and severe essential hypertension.[34] The only satisfactory areas that are at present available in the human for the study of the peripheral vascular bed are the retina and conjunctiva. It is our belief that the vascular pattern we have described is mediated by some chemical factor from the uteroplacental bed which produces the vascular spasm in the eye vessels and probably in other organs of the body. The conjunctival changes in normal pregnancy graduate into abnormal toxemic findings. This suggests that there is no clear cut dividing line between true toxemia and normal pregnancy. These variations of retinal and conjunctival circulations are additional

factors which may be used to evaluate the severity of the disease process and to further our understanding of peripheral vascular phenomena in normal and abnormal pregnancy.

Conclusions

1. The vessels of the eye (retina and bulbar conjunctiva) undergo various changes in the toxemias of pregnancy. Some of these alterations are important in evaluating the severity of the toxemic process and in furthering our understanding of this disease entity.

2. In vomiting of pregnancy retinal hemorrhages are no longer seen, probably because of improved methods in nutrition.

3. In acute toxemia severe spasm indicates an advancement of the disease process with an increasing danger of intrauterine fetal death.

4. In the non-pregnant individual or in the first trimester, retinal observations are valuable in determining the presence and extent of the vascular disease and the probability of a successful fetal outcome.

5. The presence of retinal hemorrhages and transudates is associated with high fetal mortality in both the acute and hypertensive toxemias and indicates early interruption of pregnancy.

6. Diabetic retinopathy is a serious complication which is associated with reduced growth of the fetus and maternal renal disease; it may result in permanent loss of maternal vision.

7. Variations in the peripheral vascular bed of the bulbar conjunctiva occur in normal pregnancy. Further progression of these changes is evident in the toxemias.

8. Advancing arteriolar spasm of the conjunctiva is significant as a prognostic sign in toxemia. Increasing ischemia develops in severe toxemia and reaches a maximum in eclampsia.

9. The presence of diffuse capillary tortuosity suggests underlying essential hypertension.

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ATTACKING CANCER IN A COMMUNITY*

Ninth James Ewing Memorial Lecture

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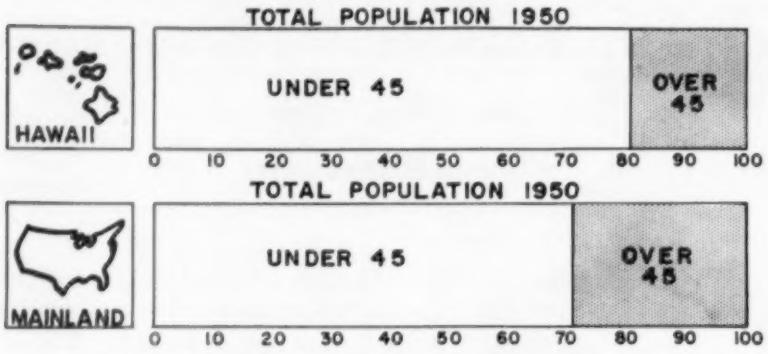
I CANNOT remember the first time I heard the name of Dr. James Ewing, nor can I remember my first acquaintance with his work in the field of cancer. However, I do remember using his principal work, *Neoplastic Diseases*, during my medical school days, and I remember being very deeply impressed with the calibre of this book. I naturally felt greatly honored and humbled by the seriousness of the invitation to give this James Ewing Memorial Lecture. As I prepared this report, I was convinced that it was entirely in accord with Dr. Ewing's philosophy as portrayed in his writings. I am sure he had a vital interest in cancer control. This is quite evident in the preface to *Neoplastic Diseases*, the last paragraph on page 8: "While confessing a deep interest in the theoretic problems which render oncology the most complex and fascinating field in pathology, *the chief object and hope of the author have been that by rendering more accessible to English readers the knowledge of tumors, he may contribute something toward the reduction of mortality from cancer.*"

It is not necessary for me to tell you that cancer is an important community health problem in most parts of the civilized world today. This is several times more true today than it was at the time Dr. Ewing first started studying neoplastic diseases. Cancer is an important health problem in Hawaii today. In this lecture, an attempt will be made to review the advances made in cancer control in Hawaii during the past seven years. I believe it is well to consider cancer control from the standpoint of the community approach, since it affects the whole community structure. Our attack on cancer has been a joint effort of the health department, the medical society, the dental society, the cancer society, the hospitals, and many other community agencies.

* Presented at the Stated Meeting of The New York Academy of Medicine, May 6, 1954. At the time this paper was presented, Dr. Quisenberry was Director, Division of Preventive Medicine, Territorial Department of Health, Honolulu, Hawaii.
Manuscript received June 1954.



Graph 1—Population Distribution—Hawaii and Mainland U.S.

Territory of Hawaii

The total population of the Territory of Hawaii is a little less than 500,000 today. In Hawaii we have had a younger population than that of the mainland United States for many years. Japanese make up approximately 37.7 per cent of the residents of Hawaii; Caucasians compose 21.4 per cent; Hawaiians and Part-Hawaiians, 17.6 per cent; Filipinos, 12.7 per cent; Chinese, 6.6 per cent; and all other racial groups, which include Puerto Ricans, Koreans, Samoans, Negroes, and others, make up 4 per cent of the total population. This makes Hawaii an ideal place to study racial differences in cancer, especially in the three largest racial groups, i.e., Japanese, Caucasians, Hawaiians and Part-Hawaiians. For many years, especially since the discovery of the islands by Captain Cook in 1778, the communicable diseases, particularly the venereal diseases and tuberculosis, were major public health problems. However, as our population has aged and the communicable diseases have been brought under control, the cancer problem has loomed larger. The distribution of Hawaii's people in the under forty-five and over forty-five age groups, as compared with the distribution for these age groups in the mainland United States in 1950, is shown in Graph 1. This picture is gradually changing as our population is aging, and also due to the fact that we are getting more older people who are moving to Hawaii in their latter years to retire.

In Table I will be found the number of deaths from cancer in Hawaii, as well as its relative position among other causes of death for

TABLE I—RELATIVE POSITION OF CANCER AS A CAUSE OF DEATH TERRITORY OF HAWAII, 1935-1953

Year	*No. of Deaths*	*Relative Position*
1935	243	7th
1936	262	6th
1937	310	4th
1938	273	4th
1939	275	3rd
1940	302	2nd
1945	359	2nd
1950	446	2nd
1953	467	2nd

the period beginning in 1935 and ending in 1953. It will be noted that not only has the number of deaths increased from 243 in 1935 when cancer was the seventh highest cause of death in Hawaii, to 467 in 1953, but it has also gone to the position of second highest cause of death, which position it attained in 1940 and it has remained there to the present, being exceeded only by heart disease.

What have we done in attacking this community health problem in Hawaii?

EDUCATION

Although we are aware that people are prone not to have regular physical examinations if left to their own devices, we feel that we have been able to stimulate the lay public in Hawaii through health education methods to have regular examinations by their private physicians. In this way early, incipient cancers are often discovered before they present any symptoms. The lay educational program is also intended to keep all members of the community informed of the early symptoms of cancer and they are encouraged to seek medical care at the earliest possible moment after symptoms begin. The curability of cancer when diagnosed early has been emphasized and thus an optimistic attitude has been produced. We believe we have already accomplished a considerable amount of life-saving through this means. Significant statistical evidence to show the exact amount of saving is not available as yet.

One example of an extensive lay educational approach has been our program for teaching women to examine their own breasts for lumps

every month according to the technique of Dr. Cushman Haagensen. The results of this program are not yet analyzable because of the comparative newness of the activity. We believe it should result in 80 to 90 per cent of all cancers of the breast being discovered at a time when they may be curable by present methods of treatment.

Another of our special lay educational programs is being conducted at the present time along with the mass x-ray survey program. For many years the mass x-ray survey for tuberculosis has been conducted in Hawaii. We are now expanding our educational work along with this so that just before the mass surveys are started, an educational program is started in the community to teach people that the chest x-ray taken in tuberculosis case-finding may detect evidence of cancer. Of course, our physicians who have examined the chest x-rays from the mass survey examinations for many years have looked for evidence of cancer or heart disease, but no attention has been given to these latter conditions until recently in the educational preparation for the x-ray survey. If evidence of cancer or heart disease is found on the chest x-ray, then procedures are instituted to see that the person gets further diagnostic tests and the proper treatment for his condition. We believe this method of attack on cancer of the lung should result in earlier diagnosis and thus save lives.

I believe I should say a word about professional education in Hawaii. We have found our practicing physicians quite eager to improve their professional work through education made possible by the circulation of regular bulletins, by the addition of the latest books on cancer to the medical libraries, and by lectures presented by various specialists from the mainland United States. We believe this should contribute materially to the early diagnosis and treatment of cancer and thus a reduction in deaths and bring about actual cancer prevention in Hawaii. We are grateful for the help we have received from members of The New York Academy of Medicine. As an example, I would like to mention the great contribution that Dr. George Pack made in coming to Hawaii in 1949. He gave much information and assistance in our cancer control program.

Investigations

In order to determine where the greatest emphasis should be placed in the cancer control program, several types of investigations have been

TABLE II—NUMBER OF CANCER DEATHS AND RATE PER 100,000 POPULATION BY RACE FOR TERRITORY OF HAWAII, 1941-1950

Race	*Population Average*	*Number of Deaths*	*Crude Death Rate*	*Adjusted* Death Rate*
All Races	462,519	3,863	83.6	141.6
Hawaiian and Part-Hawaiian	76,390	578	72.0	179.4
Caucasian	108,731	798	89.8	135.2
Chinese	31,218	335	102.1	129.1
Japanese	170,209	1,678	92.9	147.2
Filipino	57,034	244	40.9	81.5
Other**	18,937	230	115.6	141.6

* Rates adjusted to standard million U. S. Population, 1950.
** Includes Puerto Ricans, Koreans, other, and unknown races.

started. These might be listed as follows: 1) Mortality studies through death certificates; 2) A morbidity study through hospital records; and 3) Studies of place of death; i.e., at home, in hospitals and convalescent homes, etc., in an effort to determine the need for home care programs.

Some discussion on the first two types of investigations will be given in order to show how the data obtained may be used in attacking cancer in a community.

Mortality Studies: In Table II will be found the total number of cancer deaths, as well as the crude and standardized death rates, by race in Hawaii for the ten-year period, 1941 through 1950. It will be noted that this study included 3,863 deaths which occurred during the ten-year period. It should be pointed out that these data are taken from death certificates and are subject to all the errors inherent in these reports. However, the data give valid comparisons on death rates in certain groups. Since the Japanese, Caucasian, and Hawaiian and Part-Hawaiian groups are the largest in Hawaii's population, comparisons between death rates in these groups are most reliable. It will be noted that the standardized rates in all instances are higher than the crude rates. This is caused by our population being younger than the United States population average. It will be noted also that the Hawaiian and Part-Hawaiian group has a higher death rate than any other racial group. There has been considerable speculation as to why this is true. However, the most valid reason seems to be that the Hawaiian people are

TABLE III—MORTALITY RATES* PER 100,000 POPULATION FOR CANCER OF THE STOMACH AND BREAST BY SEX AND RACE TERRITORY OF HAWAII, 1941-1950

Race	Stomach			Breast
	Both Sexes	Male	Female	Female Only
All Races	42.8	53.0	27.7	12.5
Hawaiian and Part-Hawaiian	44.4	52.1	36.4	31.5
Caucasian	25.7	35.4	17.2	16.7
Chinese	22.0	22.3	20.3	15.0
Japanese	57.9	73.5	33.2	3.5
Filipino	8.4	7.4	13.2	13.2
Other**	58.0	61.4	44.4	10.1

* Rates adjusted to standard million U. S. Population, 1950.
** Includes Puerto Ricans, Koreans, other, and unknown races.

reluctant to seek medical care while their cancers are in an early stage, and actually are seen at a time when a very high percentage of their cancers are incurable; whereas the opposite seems to be true in the Caucasian and Japanese groups. This shows a very great need for more cancer education directed to the Hawaiian and Part-Hawaiian groups.

In Table III will be found the cancer death rates per 100,000 population for cancer of the stomach and cancer of the breast by sex and race in Hawaii for the ten-year period, 1941 to 1950. The most significant points brought out by this table are:

1. The death rate from cancer of the stomach in Japanese for both sexes combined is higher than in all other races. It is considerably higher than that of the Hawaiian and Part-Hawaiian and more than twice as high as the Caucasian rate.

2. When we study only the male rates, Japanese men have a rate twice that of Caucasian men and one and one-half that of the Hawaiian and Part-Hawaiian group.

3. The death rate from cancer of the stomach in Hawaiian and Part-Hawaiian women is higher than in any other group of women. It is higher than the average for women of all races, and it is more than twice the rate for Caucasian women, but it is only slightly higher than the rate for Japanese women.

TABLE IV—DISTRIBUTION OF CASES OF CANCER AND AVERAGE POPULATION BY RACE AND SEX, TERRITORY OF HAWAII, 1944-1952

	Cancer Cases		*Average Population**	
	Number	*Per Cent*	*Number*	*Per Cent*
Japanese	1,192	36.6	183,233	38.8
Caucasian	964	29.6	90,197	19.1
Hawaiian and Part-Hawaiian	447	13.7	84,375	17.9
Chinese	285	8.8	33,144	7.0
Filipino	192	5.9	60,315	12.8
Other**	177	5.4	21,027	4.4
Total	3,257	100.0	472,291	100.0

* From population estimates by Bureau of Health Statistics, Honolulu, Hawaii, 1944-1952.
** Includes Puerto Rican, Korean, Negro, Samoan, Indian.

Other workers such as Rhea,[1] Strode,[2] Steiner, [3] and McClanahan[4] have pointed out that Japanese men have more cancer of the stomach than men of other racial groups. Our figures agree in essence with the reports of these workers.

4. When we look at the death rates from cancer of the breast, we find that Hawaiian and Part-Hawaiian women have a death rate of 31.5 per 100,000 population as compared with that for all races which is 12.5; and this might be compared with the Caucasian rate which is 16.7; and most significantly, the rate of 3.5 in Japanese women. This will be discussed at some length later.

Morbidity Study: Since we are well aware of the weaknesses of mortality data, we have made a morbidity study of cancer through hospital records, which we feel is quite accurate. This study now includes 3,257 cancer cases. Each case accepted in this study has been checked by a competent medical doctor for accuracy of diagnosis. Eighty-eight per cent of the cases have histologic verification of the diagnosis made. The racial distribution of cases in this study is shown in Table IV. It is especially interesting to compare the percentage of each racial group in the total population with the per cent of the cancer cases in the particular racial groups. It can be concluded from this table that the *Chinese, Caucasian* and *other groups* have more than their share of cancers. It can be said further that the *Japanese, Hawaiian and Part-*

TABLE V—INCIDENCE RATES PER 100,000 POPULATION FOR CANCER OF THE STOMACH AND BREAST, BY SEX AND RACE, TERRITORY OF HAWAII, 1944-1952

Race	Stomach			Breast
	Both Sexes	Male	Female	Female Only
All Races	13.3	17.8	8.4	14.3
Hawaiian and Part-Hawaiian	8.6	9.6	7.7	11.5
Caucasian	11.0	16.6	6.4	33.5
Chinese	8.4	11.4	5.5	18.2
Japanese	20.7	29.1	12.1	7.1
Filipino	1.8	2.3	.6	2.4
Other*	17.6	28.2	4.3	8.6

* Puerto Rican, Korean, Negro, Samoan, Indian, etc.

Hawaiian, and *Filipino* groups do not have their share of the cancers.

From the data collected in the morbidity study, incidence rates by race and sex for cancer of the stomach and breast have been computed. These will be found in Table V. It will be noted in this table that Japanese men have a higher incidence of cancer of the stomach than any other group, and Caucasian women have a higher incidence of cancer of the breast than any other group, while Japanese women and Filipino women have lower incidence rates from cancer of the breast than any other racial groups. There were 565 cancer of the stomach cases and 289 cases of cancer of the breast in this study.

Epidemiological Studies: As stated above, both our mortality and morbidity studies have shown that cancer of the stomach is more prevalent in Japanese men than in any other racial group in Hawaii. Our studies have also shown that cancer of the breast is more frequent in Chinese, Hawaiian and Part-Hawaiian, and Caucasian women and less frequent in Japanese and Filipino women than in any other racial groups in Hawaii.

We are now working on definite plans for epidemiological studies of cancer of the stomach in Japanese men. These studies may include investigation of such factors as dietary habits, preparation of food, temperature of food when eaten (whether the men are served before the women), alcohol consumption (particularly sake consumption), and

many others. We should produce information which will be of international value in the search for the causes of cancer of the stomach. I am sure Dr. James Ewing would have been greatly interested in these studies as shown by the following quotation from *Neoplastic Diseases*, page 684 of the 4th Edition: "Stevenson analyzing English statistics observes that cancer of the alimentary tract from mouth to stomach increases as the social status of the population declines. Cramer concludes that these data prove that the causes of these forms of cancer are extrinsic connected with the dietary habits of the people and, therefore, avoidable."

Another study which we are planning, based on the statistics referred to above, is concerned with the epidemiology of cancer of the breast. Dr. Ewing was greatly interested in this subject also as evidenced by the following quotation from page 560 to 561 in *Neoplastic Diseases*, 4th Edition: "Of 628 cases of Velpeau, Gross and Winiwarter, 441 had nursed children, 187 had not. Lehmann offers statistical evidence that nursing is a prophylactic against mammary cancer. Adair secured a normal lactation history in only 8 per cent of 200 cases of mammary cancer. In some cases the disease developed in one breast, which had not been nursed, owing to some disease of the nipple. Pregnancy is without definite influence. The influence of heredity is discussed under that topic." It can readily be seen from this quotation that Dr. Ewing believed normal lactation to be a prophylactic against mammary cancer.

Practicing physicians in Hawaii have observed for a number of years that Japanese women have a much lower incidence of cancer of the breast than other women in Hawaii. Tilden[5] wrote about this in 1938. It is believed that Japanese women and perhaps Filipino women in a higher percentage nurse their children through a full period of lactation than is true of other women in Hawaii. We are planning an epidemiological study to investigate possible reasons such as lactation to determine, if possible, why Japanese and perhaps Filipino women have a lower incidence of cancer of the breast than do other women in Hawaii. We believe this study should give information which will be of international value in the fight against cancer of the breast.

Cancer Detection

Our cancer control program in Hawaii has been based on making every private physician's office a cancer detection center. We have had

TABLE VI—HAWAII CANCER SOCIETY CYTOLOGY REPORT
July 25, 1949, to March 31, 1954

Number of Patients	16,785
Number of Slides	32,798
Number of Doctors Participating	284
Number of Positive Cases	151
(Asymptomatic Uterine Cervix Cases)	35

no large detection centers. Because of the small area we cover and the closely-knit community of physicians, we have felt that our approach has been appropriate. We have endeavored to bring all of the latest diagnostic and treatment procedures to the private physician's office and assist in getting people to go to their private physicians for regular examinations for cancer, as well as for examinations when they may have symptoms suggestive of cancer. This latter part of the program has been brought about through lay education.

What We Supply to Physicians: Cytologic examinations on any body secretions, using the Papanicolaou technique, are made available to all practicing physicians in Hawaii through laboratories set up by the Hawaii Cancer Society. Any physician can prepare a slide from any body secretion and submit it to a laboratory for examination. Trained technicians stain and screen the slides and any which contain atypical cells are examined by a committee of specially trained physicians whose opinions are then transmitted to the referring physicians. The tests are performed without charge to patient or physician. All costs are underwritten by the Hawaii Cancer Society.

In Table VI will be found a summary of the cytologic tests performed in the Hawaii Cancer Society laboratory in Honolulu between July 25, 1949, and March 31, 1954. It will be noted that 284 physicians out of a total of 429 in Hawaii submitted slides to the laboratory. This will be recognized as quite a high percentage of the total physicians practicing in the Territory. There has been a gradual increase in the number of physicians using the cytology service since its establishment in 1949. This is shown in Table VII by the increase in slides submitted each year.

It should be especially pointed out that thirty-five asymptomatic

TABLE VII—HAWAII CANCER SOCIETY CYTOLOGY REPORT

	No. of Patients	*No. of Slides*	*Total Positives*	*Respiratory Positives*	*Vaginal Positives*	*Asymptomatic Vag. Positives*
July 25, 1949-Aug. 31, 1949	123	228	5	0	5	1
Sept. 1, 1949-Aug. 31, 1950	2,348	4,153	32	5	16	7
Sept. 1, 1950-Aug. 31, 1951	2,701	5,617	34	8	21	5
Sept. 1, 1951-Aug. 31, 1952	3,809	7,007	28	8	15	5
Sept. 1, 1952-Aug. 31, 1953	4,721	8,698	28	2	20	12
*Sept. 1, 1953-March 31, 1954	3,083	7,093	24	3	16	5
	16,785	32,798	151	26	93	35

* Represents an incomplete year of 7 months.

carcinomas of the cervix uteri have been picked up by the cytologic technique. These cancers were not suspected by either the patient or physician at the time the cytologic test was taken. The tests were performed as part of general cancer detection examinations. Of course, the chance of cure for these thirty-five cases is excellent. I believe we have shown that cancer of the cervix can be picked up earlier through the use of the cytological technique than by any other means. Certainly biopsies on these thirty-five unsuspected cases would have been impractical and probably would not have been done because there was no indication for them in the minds of the examining physicians. It was difficult to get positive biopsies on some of these asymptomatic cases, even after several very suspicious cytologic tests. One of the cases required eight biopsies before the cancer was found. Most of these thirty-five cases have been intraepithelial or carcinomas in situ. I believe Dr. Ewing[6] would have been greatly interested in these very early carcinomas of the cervix as evidenced by his writings on this subject.

I believe our physicians in Hawaii have been stimulated to think much more about early cancer of the cervix through the cytologic service which we have offered than they would have been inclined to do

TABLE VIII—HAWAII CANCER SOCIETY CYTOLOGY REPORT
POSITIVE CASES

July 25, 1949, to March 31, 1954

Ascitic Fluid	3
Breast Secretion	2
Bronchoscopy	3
Gastric	5
Mouth	2
Nasal	1
Pleural Fluid	4
Prostatic	—
Sputum	26
Urinary	3
Uterine Cervix	93
Miscellaneous	9
	151

otherwise, and thus they are diagnosing cervical cancer earlier than ever before. This should result in a reduction in the death rate from this type of cancer.

We have, of course, applied the cytologic technique to other types of cancer, especially those of the pulmonary system. We have endeavored to get examinations of bronchial secretions and sputum in every case of suspected cancer of the lung; and although our results are not so spectacular in the early diagnosis of cancer of the lung as they are in cancer of the cervix, we feel that we are making a contribution to the early diagnosis and treatment of this type of disease through the cytologic examination.

We have endeavored to apply the cytologic technique to gastric secretions also. Thus far our efforts have not been rewarded by a great degree of success.

In Table VIII will be found a summary by site of the 151 cases of cancer found in the 16,785 persons who had cytologic tests during the period covered by this report. The ninety-three uterine cervix cases recorded here included the thirty-five asymptomatic cases reported in Table VI. One of the breast cases is especially interesting since there was no palpable lump at the time the secretion was found to contain cancer cells.

It should be made clear that we consider the cytologic test only a screening mechanism and should always be confirmed by a biopsy if possible before treatment is instituted. The cytologic test has undoubtedly contributed materially to the early detection of cancer in Hawaii. This is especially true of cancer of the uterine cervix.

In addition to the cytologic service, a biopsy service is offered to all persons who cannot afford to pay for this procedure. The biopsy specimens are usually examined without charge by the practicing pathologists in Honolulu. However, when necessary or desirable, funds are available to pay for this service.

Consultation: Since we have a good supply of well-trained and experienced medical and surgical specialists in Hawaii, there is no shortage of consultants on a private basis. Consultation is offered free of charge to all practicing physicians through the tumor clinics which are held in the main hospitals in Honolulu. These are staffed by specialists who work on a voluntary basis.

Treatment

Most of the radium in Hawaii is owned by the Territorial Health Department. This is supplied to all practicing physicians for the treatment of cancer at a fixed rate. No charge is made for the treatment of indigent or medically indigent persons. X-ray therapy or any other type of medical care for cancer is supplied free to indigent or medically indigent persons throughout the Territory.

Cancer Prevention

As in most communities, we have been able to do very little in cancer prevention. However, I will report briefly on the few concrete things that have been done in Hawaii.

1. Education of the dentists on how cancer can be prevented through good oral hygiene has been carried on in some degree.

2. We are convinced that poor nutrition may be a very important etiologic agent in cancer of the oral cavity and in primary cancer of the liver. We are endeavoring as much as possible to prevent these cancers through nutrition educational programs.

3. We believe industrial poisons may play a part in causing primary cancer of the liver (with poor nutrition). The role of industrial poisons in the production of cancer in the pulmonary system and of the skin

has been studied. We are endeavoring to prevent these cancers through good industrial hygiene programs.

4. As a possible preventive of uterine cervical cancer, we have urged, through educational programs, that medical attention be given to cervical erosions and lacerations.

Summary and Conclusions

1. Cancer is an important community health problem in Hawaii as it is in many parts of the world today. The problem in Hawaii has increased as the population has aged and communicable diseases have been eliminated or brought under control.

2. Lay education directed toward getting every person to have regular physical examinations and report to his private physician at the earliest sign which might mean cancer has been emphasized. This should produce definite results in reducing cancer deaths. This program has caused the average lay person to be cancer-conscious and anxious to see a physician as soon as possible after symptoms which may mean cancer develop. The opposite reaction, i.e., fear of seeing a physician, has been encountered rarely. Professional education of physicians and dentists has also been emphasized.

3. Statistical studies have been made to determine the areas where most emphasis should be placed in controlling cancer in Hawaii. Epidemiological studies are being planned in attacking cancer of the stomach, which is more frequent in Japanese men in Hawaii than in other racial groups. Cancer of the breast is more frequent in Caucasian women than in other women in Hawaii. Epidemiological studies of this type of cancer are also being planned. We hope we can attract grants-in-aid from national or international organizations in order to make our epidemiological studies of cancer of the stomach and breast. We believe the data we will turn up will be of international interest.

4. The philosophy of making every private physician's office a cancer detection center has been emphasized. We have supplied to the physicians cancer detection and diagnostic aids through cytologic tests and biopsies. Consultation and the best methods of treatment are available.

5. Cancer prevention programs have been directed principally towards oral, hepatic, pulmonary, skin, and uterine cervical neoplasms. Good nutrition, avoidance of poisons, and removal of chronic irritations have been emphasized.

Through the epidemiological studies which we have planned on cancer of the stomach and the breast, we should be able to gather data on cancer prevention. I am sure this matter of cancer prevention is entirely in accord with the philosophy of Dr. James Ewing as revealed by the following quotation from his writtings:[7] "So it seems to be a royal summons, this call to join the heroes and martyrs of history. It is a good deal that they are deemed worthy of the call. The great majority of natural deaths are *preventable*, if we would go back and do the right things at the right time. They are none the less inevitable with our human foresight. Don't entertain any doubts of this fact. We do the best we can at the time and the right choice is our good fortune, while failure is absolutely beyond our control."

6. I must tell you again how greatly honored I feel in being invited to give this Annual James Ewing Memorial Lecture on Cancer, and I would like to express my appreciation, especially to Dr. Elise L'Esperance and the members of her committee who extended the invitation to me. As a final tribute to Dr. Ewing, I will quote from the presentation of Dr. L'Esperance[7] before the Section on Historical and Cultural Medicine of The New York Academy of Medicine, on November 9, 1949, in which she said: "The influence of his life, its human understanding and high ideals have left their imprint on all who knew him. His life work has given to American medicine an inspiration in cancer research that has established on a firm foundation the broad vision of cancer control today. There exist in every age masterful men who are masterful because they see with clear vision the course of events and fearlessly act upon the forecast. We wonder and cannot explain why these souls of rare genius have no successor of equal powers."

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MEDICAL RESEARCH FORUM

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ABSTRACTS

Cirrhosis of the Liver with Portal Hypertension in Cystic Fibrosis of the Pancreas

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It is known that some infants and older children with cystic fibrosis of the pancreas are found at autopsy to have scattered through the liver small areas of biliary cirrhosis. Also, occasional patients are found at postmortem to have extensive hepatic cirrhotic changes. It has not been realized, however, that the localized liver lesions which are not clinically manifest may progress to widespread cirrhosis of the liver with hepatosplenomegaly and portal hypertension.

The first lesion is a biliary cirrhosis with concretions, focal tissue destruction and no diffuse architectural remodeling. This may be limited to a few areas or may become extensive. Even in the latter case the scattered character of the lesions is such that even though a significant amount of parenchyma is involved, there are no clinical or laboratory symptoms. In particular, there is no jaundice. At autopsy in such patients the liver appears grossly and deeply lobulated, real hepar lobatum. The microscopic picture is striking and distinctive. There is diffuse portal cirrhosis with disorganization characterized by: biliary proliferation, inflammatory reaction, "concretions" of amorphous eosinophilic material plugging the bile ductules and absence of bile stasis. The nature of the concretions is not clear, but morphologically and histochemically they resemble those in the pancreas which have been thought to be formed by inspissated secretions.

As it progresses, the cirrhotic process leads to considerable distortion in the architecture of the liver parenchyma and in some cases hepatic fibrosis becomes so diffuse as to render difficult on biopsy the distinction from the late stage of other types of cirrhosis. The remodeling of the liver is such that portal hypertension eventually develops. It is at this stage that the condition becomes clinically manifest with the appearance of hepatosplenomegaly and later hypersplenism, gastrointestinal bleeding, ascites or a combination of the three. The liver chemistries are often abnormal at this time. Patients may require surgery in an attempt to relieve excessive pressure in the portal system by means of a splenorenal or portocaval shunt.

Biliary cirrhosis with concretions of the type described has been present in 11 per cent of the sixty-three patients with cystic fibrosis of the pancreas that came to autopsy at Babies Hospital. Another seven have had cirrhosis with portal hypertension or about 3 per cent of the 286 cystics seen to date. All of these seven patients had pulmonary

and sweat gland involvement. In five of the cases complete exocrine deficiency of the pancreas was present, but the remaining two had normal pancreatic function. Three were operated and had a shunting procedure performed by Arthur H. Blakemore.

It should be stressed, therefore, that the hepatic area is not infrequently involved in cystic fibrosis of the pancreas. Some of such patients go on to manifest cirrhosis of the liver with portal hypertension, accounting for about one-third of pediatric cases with this clinical picture. From the diagnostic standpoint the combination of abnormally high sweat electrolytes and of chronic pulmonary disease should lead to the suspicion of cystic fibrosis even in the absence of pancreatic deficiency.

Thorazine-Rauwolfia Serpentina Combination in the Treatment of Essential Hypertension*

(Preliminary Report)

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Essential hypertension is treated medically, today, with more than two dozen preparations, most of which cause disturbing side effects or fail to produce the desired response. This preliminary report is concerned with the results of treatment carried out over a period of one year, on one hundred patients, using a combination of Thorazine and Rauwolfia serpentina. Thorazine is a non-barbiturate central depressant agent;[1-10] Rauwolfia serpentina acts directly on the hypothalamus and inhibits the sympathetic system. The latter, has been used quite extensively for the treatment of essential hypertension.[11, 12]

One hundred patients (non-hospitalized) were placed on varying combinations of Thorazine and Rauwolfia serpentina. The optimal dosage was found to be 15.0 mg. of Thorazine and 50.0 mg. of Rauwolfia serpentina, given orally three times daily. Clinical deportment, blood pressure readings, renal function, eye ground examinations, heart size and other usually accepted criteria were studied; patients were observed at varying intervals ranging from daily to weekly.

Preliminary study of the results suggest that the combination of Thorazine-Rauwolfia serpentina is a potent anti-hypertensive agent, with no adverse effects; 85 per cent of the patients with mild hypertension, 70 per cent with moderate hypertension and 60 per cent with severe hypertension were benefited by the use of this combination. Thorazine, used alone, depressed blood pressure for approximately two weeks, after which the blood pressure reverted to its base line. Rauwolfia serpentina, alone, is effectual in the management of mild hypertension. Its action appears to be synergistically enhanced and prolonged by combining it with Thorazine.

This preliminary report describes a new therapeutic combination which gives promise in the management of essential hypertension, without the accompanying adverse and/or toxic effects of the presently used preparations. The site of action of this combination in the brain is the subject of present investigation.

* Thorazine—Brand of Chlorpromazine, Smith, Kline & French Laboratories.

TABLE I.—SUMMARY OF RESULTS

Preparation	*Response*	*Duration*	*Remarks*
PLACEBO	Fair	4-10 Days	No significant drop in BP
THORAZINE (15.0 mg. TID)	Poor	10-14 Days	BP drop rarely persists more than 14 days
RAUWOLFIA (50.0 mg. TID) (Whole root)	Good in mild and controlled cases	10-14 day lag; persists during therapy	Good therapy in mild cases; few side effects with this dosage
Combination of: THORAZINE (15.0 mg.) RAUWOLFIA (50.0 mg.) TID	Mild cases: Excellent Mod. cases: Excellent Sev. cases: Good	during therapy	Synergistic enhancement: no significant side effects; smaller doses possible with persistence of therapy

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Thyroidal Uptake and Plasma Level of Radioactive Iodine in the Diagnosis of Untreated Hyperthyroidism

ROBERT A. NEWBURGER, SOLOMON SILVER, STEPHEN B. YOHALEM and SERGEI FEITELBERG

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The diagnosis of hyperthyroidism in previously untreated patients can often be made quite readily by consideration of the history, physical findings, and easily available laboratory tests. Frequently, however, hyperthyroidism is far from obvious, and conversely may be absent despite the display of some of the characteristic signs and symptoms. Since the introduction by Hertz in 1938 of the use of radioactive iodine for the diagnosis of thyroid disorders, various improvements in technique have been developed. At the present time the uptake of radioactive iodine by the thyroid gland is measured twenty-four hours after a suitable tracer dose. In 1950 we pointed out the diagnostic value of determinations of the level of protein-bound I-131 in the plasma at seventy-two hours after the tracer dose. The purpose of this paper is to present the results of these two tests in a series of about 500 individuals of whom about 100 were considered undoubtedly hyperthyroid and the balance euthyroid. None of these had been subjected to surgery or had received therapeutic doses of I-131. Also excluded were all patients receiving anti-thyroid drugs, iodides or thyroid extract, cortisone or ACTH, or who had been subject to diagnostic procedures involving the use of radio-opaque iodine-containing compounds.

Results: The results of the PBI-131* and of the uptake measurements have been studied graphically by means of frequency distribution curves. These indicate clearly the very considerable overlap in uptake measurements between normal individuals and hyperthyroid patients. The overlap is much smaller in the figure showing plasma levels of PBI-131.

Statistical analysis of the results of these two tests when studied for the likelihood of error in diagnosis indicates that at the level of PBI-121 of 0.26 per cent of the administered dose per liter of plasma the total errors in 500 cases were 1.6 per cent. Similar treatment of the uptake data indicates that the same accuracy can be obtained only by accepting a doubtful range between 42 and 69 per cent and calling only those below 42 per cent normal and those above 69 per cent hyperthyroid. This leaves 27 per cent of the patients undiagnosed by this technique. When uptakes within this range are encountered, additional diagnostic tests are necessary, such as the PBI-131 at seventy-two hours.

Summary and Conclusions: Various methods for the diagnosis of hyperthyroidism have been reviewed. The value of studies with radioactive iodine, by means of both twenty-four hour thyroidal uptake and seventy-two to ninety-six hour plasma levels, has been assayed. A reliable method for determination of the plasma level with the aid of the well-type crystal scintillation counter has been described. Evidence has been presented which indicates that twenty-four hour uptake measurements between 42 and 69 per cent must be considered doubtful if an over-all accuracy equal to that of the blood level method is desired. Seventy-two to ninety-six hour plasma levels above 0.26 per cent of the administered dose per liter of plasma may be considered hyperthyroid in untreated individuals. Levels below 0.26 per cent are usually found only in euthyroid individuals.

* PBI-131 is defined as per cent of administered dose of I-131 bound to the proteins per liter of plasma, after 72 hours.

Occurrence of Myeloid Leukemia in Patients with Metastatic Thyroid Carcinoma Following Prolonged Massive Radioiodine Therapy

S. M. Seidlin,* Edward Siegel, B.S., S. Melamed and A. A. Yalow, Ph.D.

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At Montefiore Hospital two cases of subacute leukemia have occurred in a series of sixteen patients with metastatic thyroid carcinoma intensively treated with radioiodine. This series covers the period from 1940 to 1954. Eleven of the group are dead. The radioiodine received by these patients ranged from 195 mc. to 2290 mc. over a six-month to nine-year time interval. The five patients still living have been treated with 275 to 1030 mc. I^{131} over a period of from one to six years.

Patient J.F., a white male of sixty-two, was treated for four years. He received a total of 1455 mc. I^{131}, which delivered a blood radiation dose of about 600 rad. Five months before death, he developed anemia without leukopenia. Two months later episodes of "virus pneumonia" began to occur with persistent low-grade fever. His cervical lymph nodes became enlarged and blood began to appear in the stools. During the last month of his life, the peripheral blood showed anemia, scarcity of blood platelets and presence of myelocytes and myeloblasts. He died in 1951 with a clinical picture of subacute myeloid leukemia. Postmortem studies demonstrated, among other findings, myelogenous leukemia involving bone marrow, spleen, liver and lymph nodes; also anaplastic carcinoma of thyroid metastases to cervical lymph nodes, skull, spine and lungs.

Patient B.L., a white female of sixty-six, was treated for about five years. She received a total of 1600 mc. I^{131}. The patient had transient leukopenias since the beginning of radioiodine treatment. The leukopenia became more marked in the last three years, and was accompanied by anemia. Since June 1953 her differential count began to show "abnormal forms" and high "lymphocyte" counts. In September 1954 the WBC count began to rise rapidly with a high proportion of myelocytes and myeloblasts. Both clinically and hematologically she exhibited the picture of acute myeloid leukemia. At autopsy, among other findings, there was evidence of leukemic infiltration of the spleen, liver and bone marrow.

We do not claim that a causal relationship between radioiodine therapy and leukemia is definitely established by these results. However, the occurrence of these two cases in a series of sixteen patients makes the presumptive evidence strong for the correlation. Moreover, the experimental production of leukemia in animals by radiation, the frequent occurrence of leukemia among radiologists as compared to other physicians, and the high incidence of chronic myelogenous leukemia among the survivors of the Hiroshima and Nagasaki atomic explosions—all these facts corroborate the evidence for a relationship between massive radioiodine therapy and the development of leukemia.

There is a striking absence of leukemia among the thousands of hyperthyroid patients treated with radioiodine during the last fourteen years. For hyperthyroid patients the radiation administered is a small fraction, the order of 1/100, of that given to patients treated for metastatic thyroid carcinoma. The time of exposure is also shorter. This would seem to indicate that the minimum necessary requirements for the development of leukemia in susceptible individuals are either high levels of radiation delivered over a short interval of time or radiations of low intensities extending over a protracted period.

In the two cases we are now reporting the factors of both radiation dose and time of exposure were large.

* Deceased, January 2, 1955.

*The Significance of the Depression of Individual Complement Components for the Differential Diagnosis of Renal Diseases**

KURT LANGE, EUGENE J. WENK and
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Serum complement values reflect an activity rather than the presence of a uniform substance. There are at least four components of complement (C'1, C'2, C'3 and C'4) which can be quantitatively estimated in the serum of human beings and experimental animals. Lowering of serum complement levels is usually due to the lowering of one of the components which becomes the limiting factor of the total activity. Typical immune precipitates remove from serum mostly component C'4 and, to a lesser extent, C'2, while the levels of components C'1 and C'3 remain unaltered.

When isolated rat kidneys are perfused with fresh rat serum and nephrotoxic antiratkidney rabbit sera are added in small amounts, the complement level rapidly falls after passage through the kidney. These nephrotoxic sera were shown to produce in the intact animal a nephrotic syndrome in a high percentage of cases. When the perfusing sera were analyzed for individual complement components a lowering of component C'2 and, to a lesser extent, of C'4 was found. An identical pattern of removal of complement components was found in the sera of rabbits in which experimental nephritis was produced by the injection of nephrotoxic duck sera.

Ten cases of acute human glomerulonephritis all showed a marked lowering of complement activity. When these sera were analyzed for individual complement components, component C'4 was always found to be the limiting factor. A similar lowering of complement activity was found in four cases of lupus erythematosus disseminatus with an identical pattern of complement components.

When sera of ten patients with the nephrotic syndrome were studied in a similar way, all were found to have lowered complement activity. When they were analyzed, however, for individual complement components, it was found that in all of them C'2 was the limiting factor while C'4 occasionally was lowered but to a lesser degree. This was the case irrespective of whether or not an underlying glomerulonephritis could be demonstrated.

One is thus able to decide from a serum complement determination whether active disease is present and in addition, by determining individual complement components, whether one is dealing with an acute glomerulonephritis or a nephrotic syndrome.

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Clinical Experience with the Injection of Streptokinase Intramuscularly in the Treatment of Infections and Edema

JOSEPH M. MILLER, JOHN A. SURMONTE, MILTON GINSBERG* and FRANK A. ABLONDI, A.B.**

The ability of trypsin to influence the inflammatory reaction has been demonstrated. This phenomenon may be mediated by plasmin. It was of interest to determine whether an anti-inflammatory effect or an anti-edema effect could be produced by the intramuscular administration of streptokinase, a known activator of plasminogen. The features of the inflammatory reaction which localizes infection are barriers to the effective action of the humoral, chemotherapeutic and antibiotic agents. The removal of any of these factors should aid bodily defenses and drugs to attack bacteria more successfully. Observations in patients with infections and edema indicate that profound changes in reversing these states can be effected by the intramuscular administration of streptokinase. The mechanics of the action are at present presumptions and not proven by microscopic examinations or chemical analyses. The anti-inflammatory and anti-edema effects of streptokinase were investigated in three ways. In the first, streptokinase was added to the blood plasma of the patient. In the second, streptokinase was given intramuscularly. In the third, streptokinase was added to an aqueous solution of polyvinyl pyrollidone in the hope that the latter would act as a retarding agent in the absorption of the former. The results in sixty-eight patients, a small number of whom were controls, are analyzed. The results in general have been excellent. Treatment with streptokinase given intramuscularly must be accompanied by the administration of a chemotherapeutic or an antibiotic agent. The use of streptokinase given intramuscularly is not a substitute for sound surgical treatment. Further investigation in the use of streptokinase given intramuscularly is indicated.

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Debridement of Burn Slough by Peptidases Recovered From Clostridium Histolyticus

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Three enzymes have been recovered from the fermentation of Cl. histolyticum by a second ammonium sulfate fractionation. These are 1) a proteinase obtained at a 17-20 per cent concentration of ammonium sulfate, 2) a collagenase obtained at 23-29 per cent concentration and 3) peptidases obtained at 30-35 per cent concentration. Previously, two fractions, a collagenase and proteinase were isolated, the first by a single ammonium sulfate fractionation and the second by methanol precipitation. Both enzymes were shown to be capable of separating burn slough. The proteinase was found to attack denatured collagen while the collagenase liquefied undenatured collagen. The addition of a small amount of the collagenase to the proteinase aided the proteinase in removing slough. This result was not unexpected because burned skin consists of both undenatured and denatured collagen.

Multiple eschars in left groin. Most caudal eschar is beginning to separate but the ones at the top are still intact and very adherent.

That the peptidase obtained by the new method of separation was also capable of removing burn slough came as a complete surprise, however. Peptidases are only capable of breaking down peptides into amino acids. For this reason the peptidase fraction was not even tested against burn buttons until after the more potent proteinase obtained by the second fractionation method was thoroughly tested. Then it was discovered to be a very active agent. As little as 0.25 mg. per cc. removed burn slough within twenty-four hours, when 1 cc. was injected under a burn 1 cm. in diameter. This occurred without causing hemorrhage in at least sixteen different rabbits, and a healthy base was left behind that quickly granulated. When injected intracutaneously in normal skin, a slight redness developed for twenty-four hours but no ulceration occurred. Mice have been given 0.2 cc. intravenously in doses from 0.12 to 2.0 mg. per cc. to test its general toxicity. At the highest level, the mice receiving 2.0 mg. per cc. were sick for twenty-four hours with rapid respiration and were semi-stuporous for a while but then recovered. Those given 1.0 mg. per cc. were unaffected. The peptidase of the Cl. histolyticum fermentation does not digest burn slough in vitro. Hence it must be assumed that it activates a tissue enzyme.

0.5 mg. per cc. has been used to treat a sloughing lesion on the foot of a diabetic; 10 cc. were used to wet the dressing and left for twenty-four hours. No ill effects

Three days later. Entire slough removed. One section with each injection. First, the most caudal, then the intermediate and lastly, the most cephalad where there is a deep defect in the subcutaneous tissue. All three promptly healed.

were encountered, the patient's temperature did not rise nor were there any changes in his urine. Symptomatically, the foot felt better according to the patient's own volunteered statement. On inspection, most of the slough was removed and there were pink healthy granulations everywhere.

Another patient has received injection into slough that occurred in the left groin following a gland dissection. The first dose given was 4 cc. and the second dose 10 cc. No complications resulted from either amount. The first injection resulted in removal of part of the treated slough and distinct liquefaction without separation of the rest. The second injection resulted in complete separation of the treated portion. Pyocyaneus was present in this hard slough that was deeply adherent and attached, although it was twenty days old.

Peptidases have a wide distribution in the human body. Red blood cells, normal skin and granulation tissues contain peptidases. Peptidases are also found in yeast fermentations and in erepsin secreted in the small intestines. There are at least twelve peptides that can be attacked by them. Certain peptidases are capable of attacking only single peptides, while others attack combinations. Therefore they are spoken of as di, tri and carboxy peptidases. The peptidase found in erepsin does not remove burn slough hence the peptidase obtained from the fractionation of the fermentation of Cl. histolyticum must be a very specific peptidase.

Our future experimental approach is to characterize this peptidase as accurately as possible by testing it against numerous peptides, recognized by paper chromotography. As soon as the nature of this particular peptidase is determined, an attempt will be made to find a plentiful, cheaper source.

Pathological sections made of the burn slough treated with peptidase will be compared to the leukocytic reaction occurring about the untreated burn slough. Histochemistry will be employed to determine whether differences can be demonstrated.

Clinical Evaluation of the Tobacco Ballistocardiogram

LEON PORDY

The Mount Sinai Hospital, New York

Clinical decision as to the detrimental cardiovascular effects of smoking in individual patients has rested heretofore on the personal opinion and prejudices of the examining physician. Electrocardiographic alterations after smoking have proved to be of decisive value only rarely. Conversely, the ballistocardiographic response to smoking appears to be a sensitive objective index in this regard.

The effects of smoking on the direct ballistocardiogram were investigated in one hundred unselected private patients. Complete cardiac survey was made including electrocardiogram, fluoroscopy and/or chest roentgenogram, ballistocardiogram and exercise tolerance test. The ballistocardiogram was recorded in the basal state after overnight abstinence from smoking. Using the Dual ballistocardiograph, direct Dock-type tracings were taken in slight held inspiration, deep inspiration and deep expiration. Both photoelectric (displacement) and electromagnetic (velocity) records were taken in all cases. The patients were then asked to smoke at their customary rate, usually two standard cigarettes. Ballistocardiograms were then recorded again immediately after cessation of smoking.

For purposes of analysis, the cases were divided into two groups: first, normal control patients with no clinical evidence of organic heart disease and second, patients with angina pectoris due to arteriosclerotic coronary artery disease. The results disclosed that in sixty-six non-cardiacs the tobacco ballistocardiogram was abnormal in seventeen, borderline in six and normal in forty-three. In thirty-four cardiacs with angina pectoris the tobacco ballistocardiogram was positive in eighteen, borderline in one and negative in fifteen. Thus the procedure was abnormal in 26 per cent of non-cardiac patients as against 53 per cent of the cardiac group.

In several instances in this investigation, various commercially available filter cigarettes were tested as well as the standard types. The use of filters definitely affected the tobacco ballistocardiographic tests, in that the alterations noted previously with standard cigarettes were either minimized or abolished in many cases. In a few cases with abnormal tobacco ballistocardiograms, skin tests for tobacco allergy were negative.

Follow-up studies of sixteen patients who discontinued smoking after positive tests revealed uniform clinical improvement with complete cessation of chest pain in seven. The tobacco ballistocardiogram is presented as a valuable and objective screening test for routine application in clinical cardiac practice.

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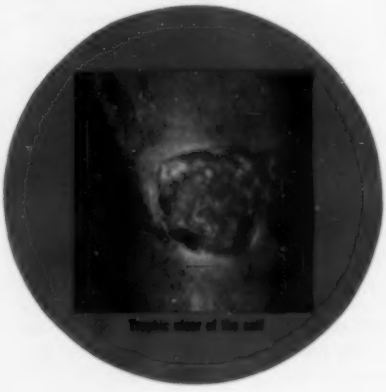
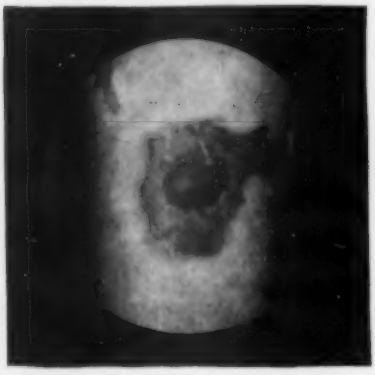


Trophic ulcer of the calf



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Innerfield, I., *Trypsin Given Intramuscularly in Chronic, Recurrent Thrombophlebitis, J.A.M.A.*, 156:1056-1058 (Nov. 13) 1954. Golden, H., *Intramuscular Trypsin, Its Effect in 83 Patients with Acute Inflammatory Disorders, Del. State Med. J.*, 26:267-270 (Oct.) 1954.

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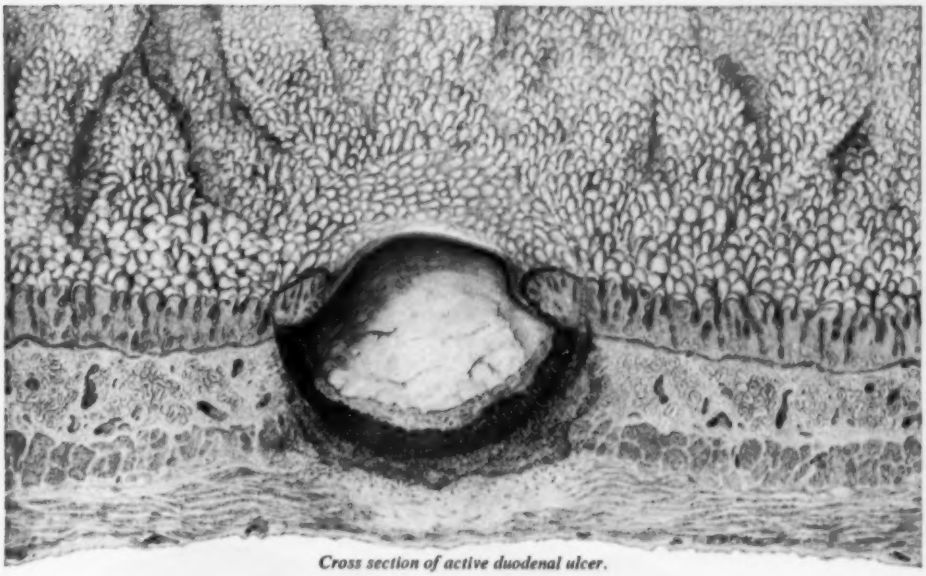

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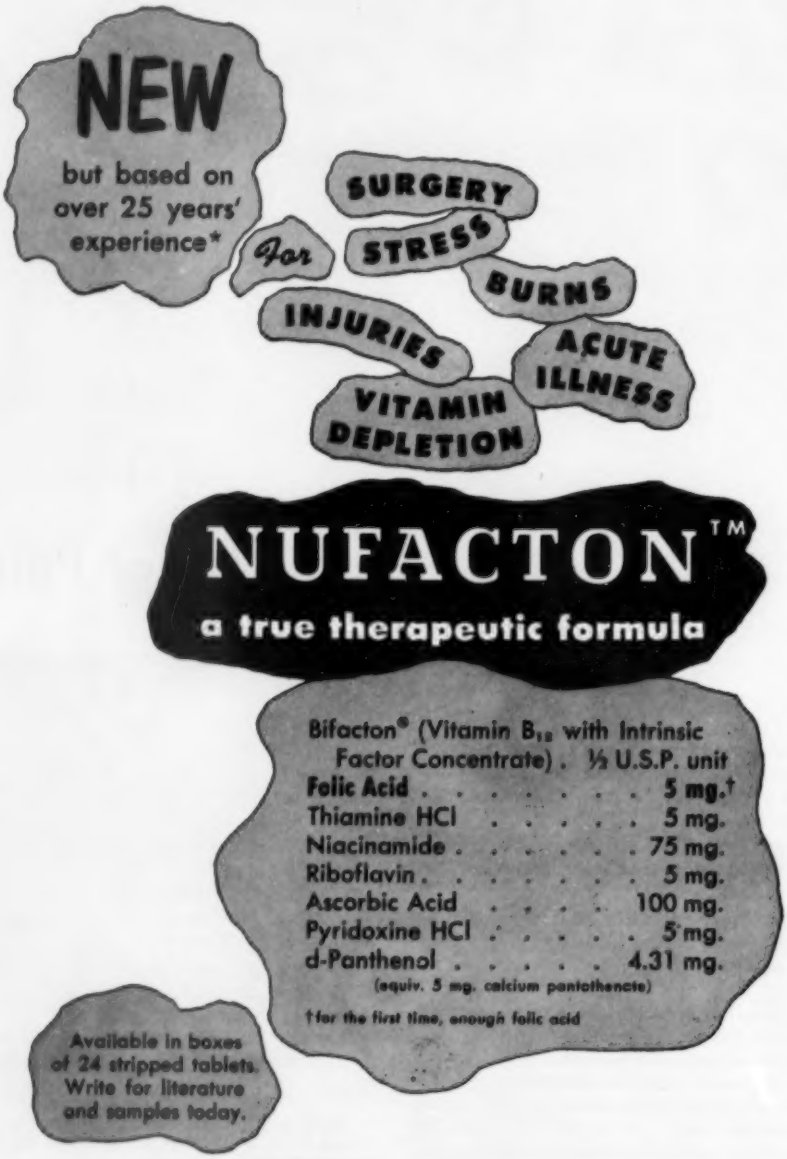

*Spies, T.D., et al. Postgraduate Med., March, 1955

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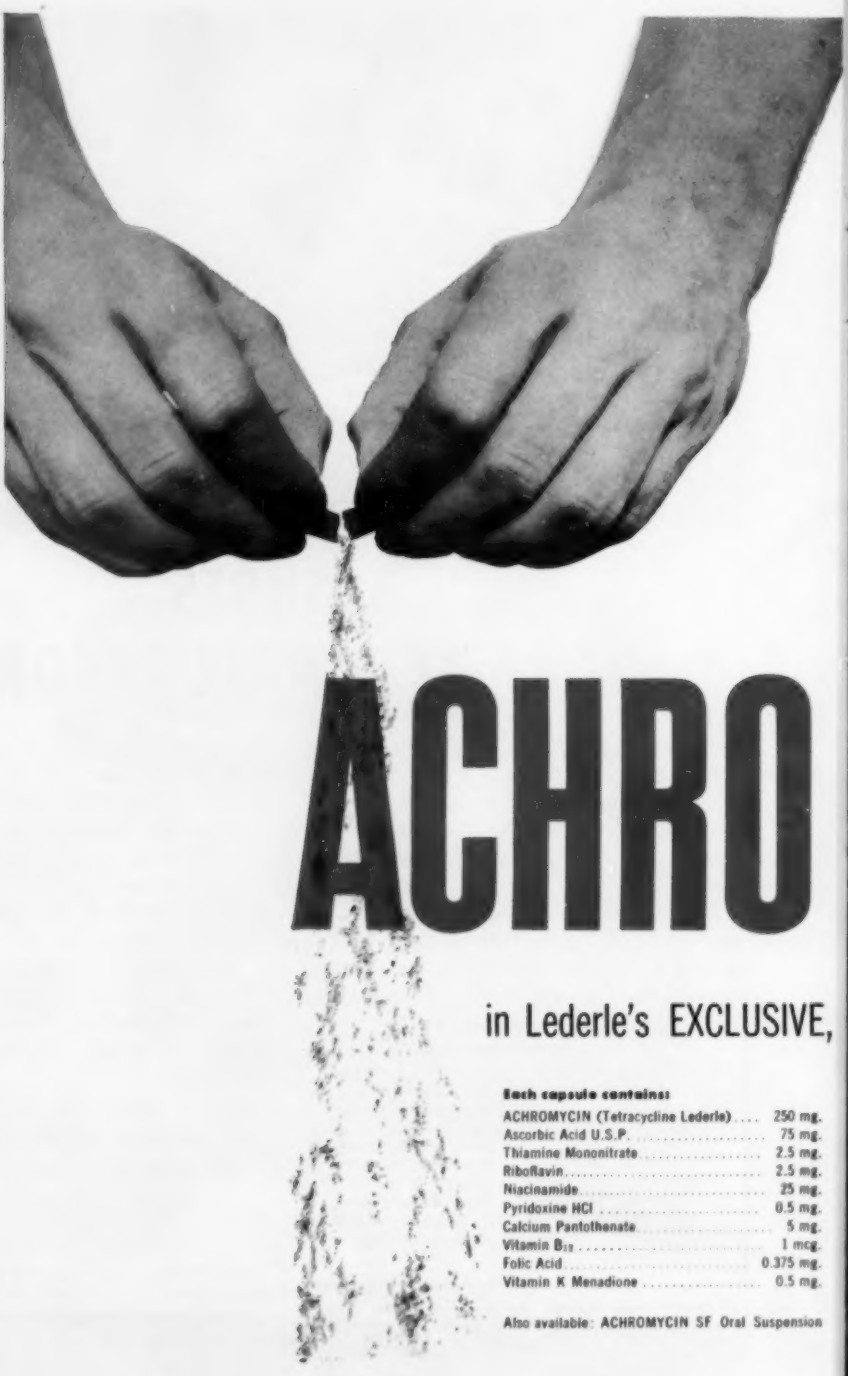

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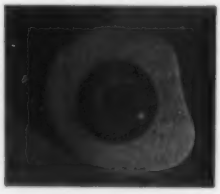

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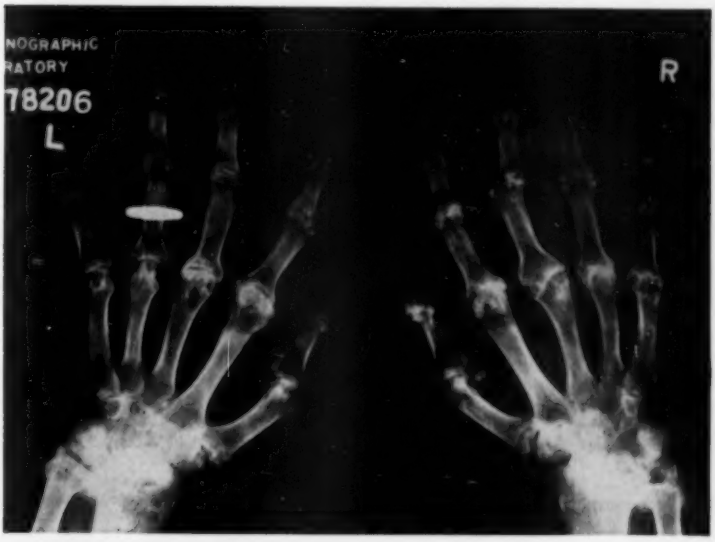

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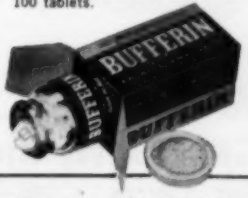

References: 1. Fremont-Smith, P.: In press. 2. J.A.M.A. 141: 124, 1949. 3. M. Times 81: 41, 1953.

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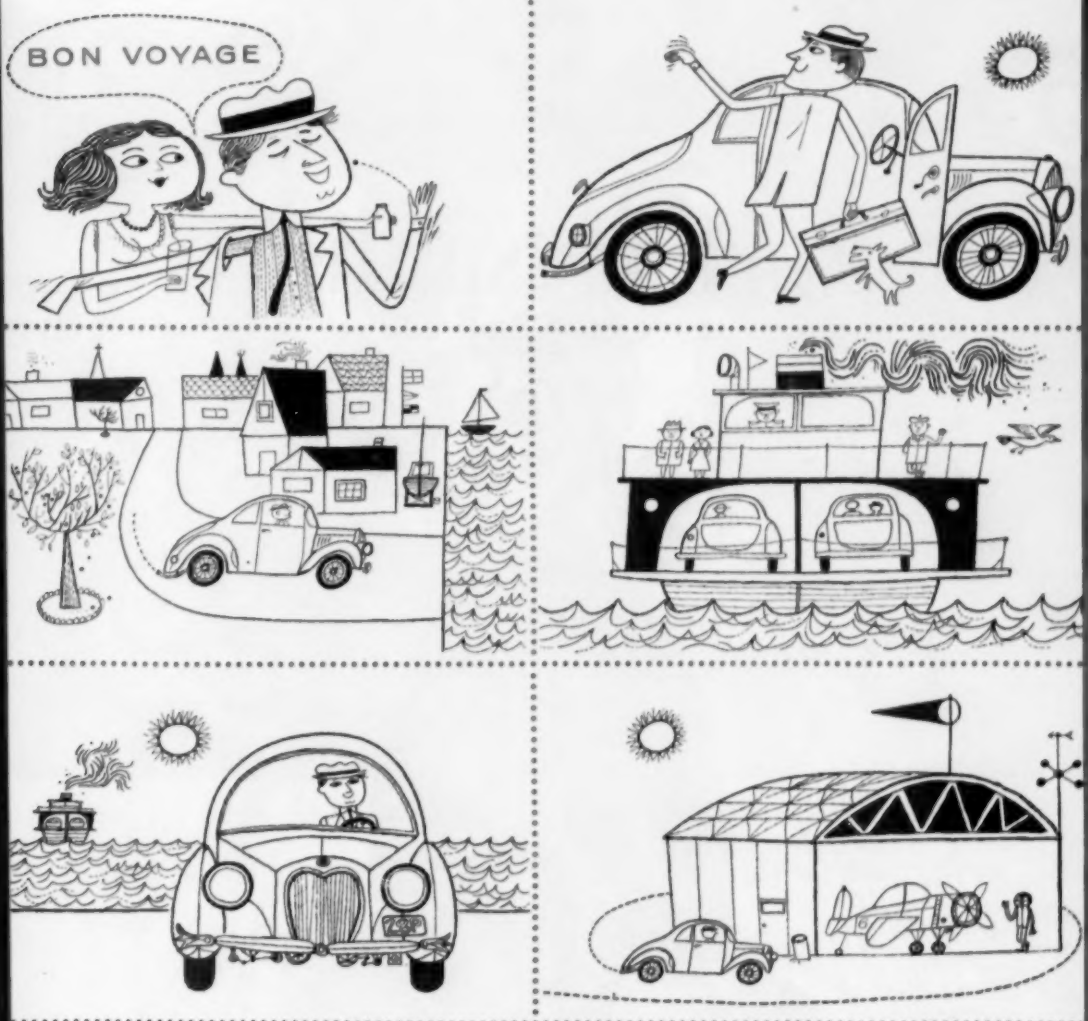

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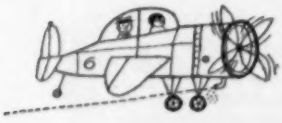

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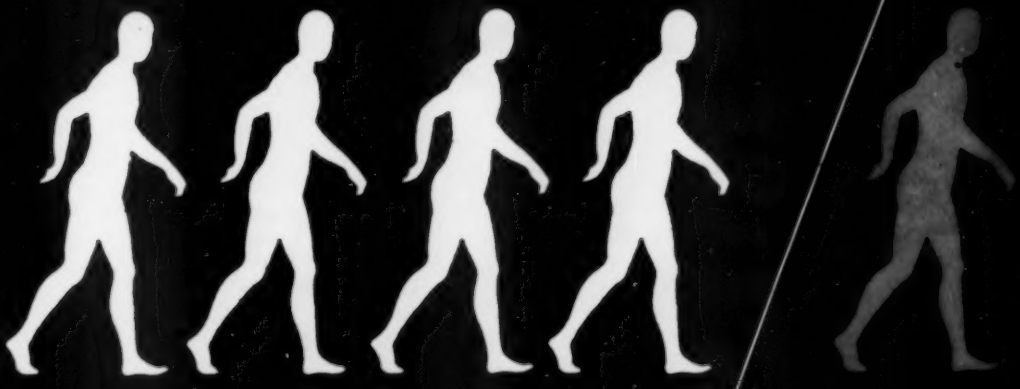

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1. Winsor, T., Humphreys, P.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
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4. Russek, H. I., *et al.*: Am. J. M. Sc. 229:46 (Jan.) 1955.

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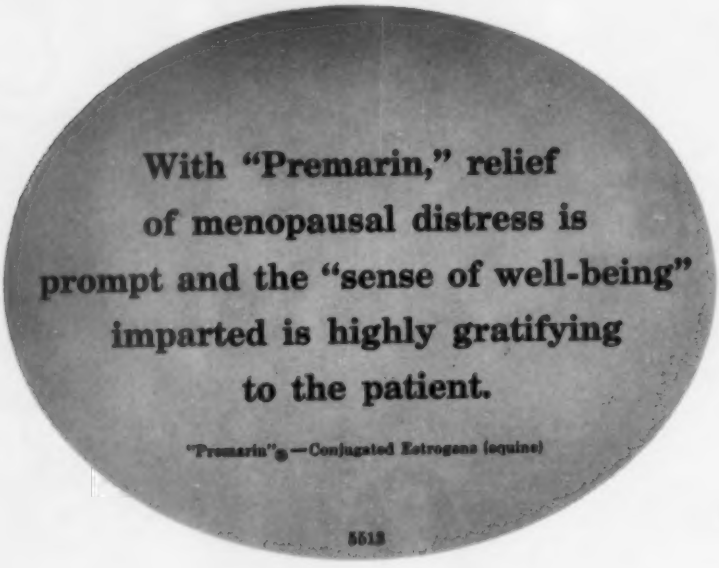

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References: (1) Lawrence, E. D.; Doktor, D., and Sall, J.: Angiology *2*:405, 1951. (2) Rottino, A.; Boller, R., and Pratt, G. H.: Angiology *1*:194, 1950. (3) Boller, R.; Rottino, A., and Pratt, G. H.: Angiology *3*:260, 1952. (4) Pratt, G. H.: Surg. Clin. North America *33*:1229, 1953.

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[1]Nesbit, R. M. and Lapides, J.: J. Urol. *63:* 1109 (1950).
[2]Richardson, J. F. and Rose, D. K.: J. Urol. *63:* 1113 (1950).
[3]Nesbit, R. M. and Nesbitt, T. E.: U. Mich. Med. Bull. *18:* 225 (1952).
[4]Zink, O. C.: (Private report dated May 12, 1952).

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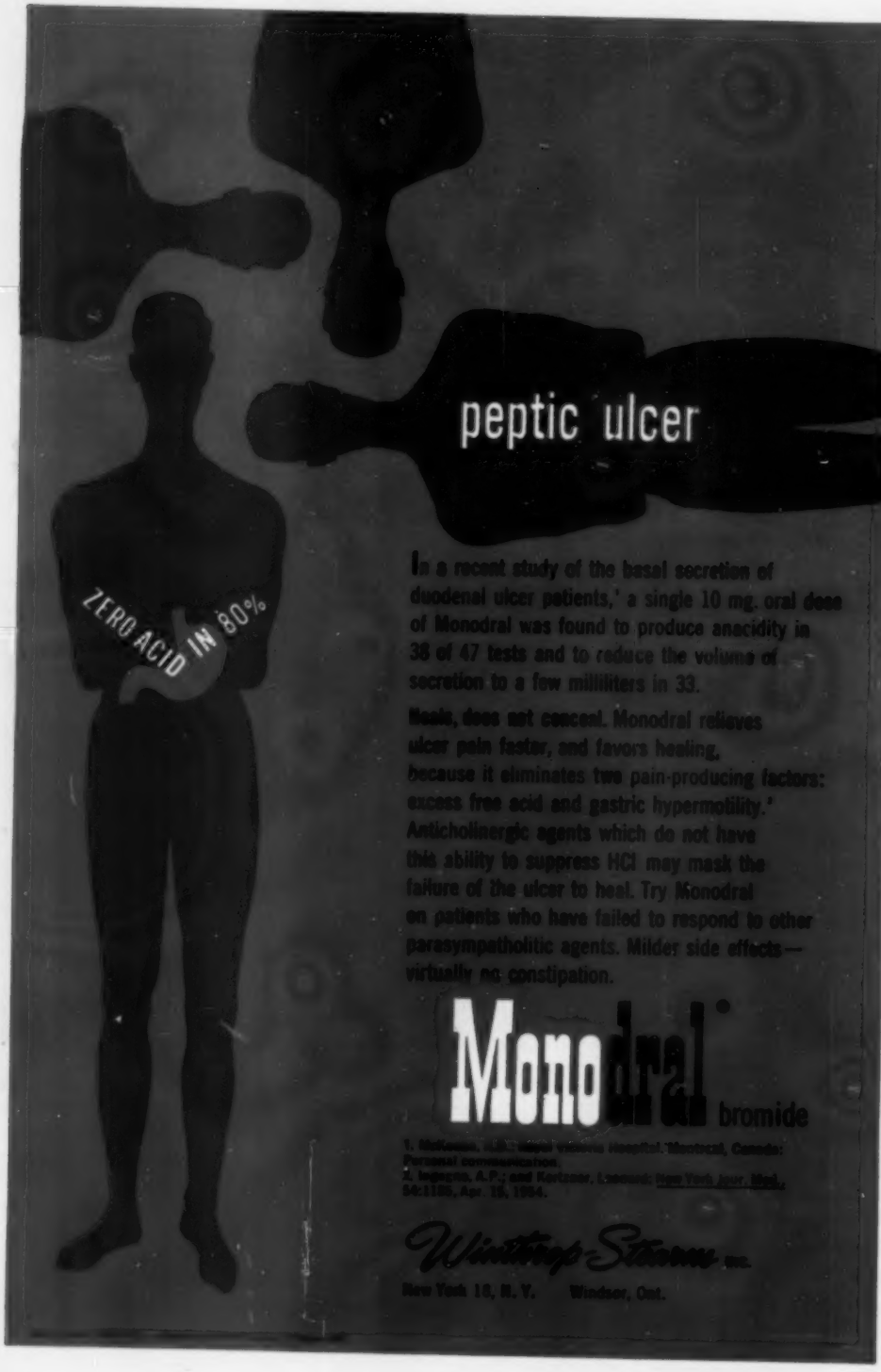
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1. McKenna, W.B.: Royal Victoria Hospital, Montreal, Canada: Personal communication.
2. Ingegno, A.P., and Kortzow, Leonard: New York Jour. Med., 54:1105, Apr. 15, 1954.
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